Strengthening evidence for exercise advice in spondyloarthritis

By

Janet Ruth Millner (Grad. Dip. Phys.)

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Declaration of originality

The thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of ethical conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Statement of Co-authorship

This thesis includes papers for which Janet Millner (JM) is not sole author. JM took the lead in this research in that she implemented the research, collated and analysed the data and wrote the manuscripts. However, she was assisted by the co-authors. The contributions of each author are detailed below.

1. The paper reported in chapter 3:

Millner JR, Barron JS, Beinke KM, Butterworth RH, Chasle BE, Dutton LJ, Lewington MA, Lim EG, Morley TB, O'Reilly JE, Pickering KA, Winzenberg TM, Zochling JM. Exercise for ankylosing spondylitis: An evidence-based consensus statement. Seminars in arthritis and rheumatism. 2016, 45:4:411-427

The contribution of each author:

JM was the primary author and contributed approximately 80% to the research project and subsequent paper. JM contributed to the conception and design of the study, obtained approvals for the study, led and coordinated the writing group, acquisition of data and data management; with JZ undertook all data analyses and interpreted data; composed the drafts of the manuscript, and coordinated revision of the manuscript.

JZ with JM conceptualised, designed and coordinated the study, led the face to face writing group meeting and contributed to data interpretation and drafting and revision of the manuscript.

TW contributed to the design of the study, data interpretation and drafting and revision of the manuscript.

JB, KB, RB, BC, LD, ML, EL, TM, JO'R and KP were members of the consensus panel. They reviewed papers, extracted data and contributed to the consensus process, development of recommendations and manuscript revision.

All authors critically revised the manuscript for important intellectual content, and read and approved the final manuscript.

2. The paper reported in chapter 5:

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JM was the primary author and contributed approximately 70% to the research project and subsequent paper. JM coordinated the study, acquired and managed the data; with KW undertook all data analyses and contributed to data interpretation; composed the drafts of the manuscript, and revised the manuscript.

JZ was Chief Investigator for the Tasmanian Ankylosing Spondylitis Study, was responsible for obtaining approvals and the design and conduct of that study. For

the MRI sub-study, JZ obtained the imaging resources, and contributed to the conceptualisation and design of the study and interpretation of data.

JH contributed to the conceptualisation and design of the study, establishing the MRI protocol for the trunk muscles, consulting on image measurement procedure, assistance with interpretation of results and revision of the manuscript.

KW with JM undertook all data analyses and contributed to data interpretation, provided statistical expertise, and manuscript revision.

TW contributed to the design of the study, interpretation of the data and revision of the manuscript.

We the undersigned agree with the above stated "proportion of work undertaken" for each of the above published (or submitted) peer-reviewed manuscripts contributing to this thesis:

Signed:

Professor Tania Winzenberg
Supervisor
Menzies Institute for Medical Research
University of Tasmania
Date: 11 October 2018

Professor Alison Venn
Director
Menzies Institute for Medical Research
University of Tasmania
Date 15/10/2018

Abstract

‘Axial spondyloarthritis’ (axSpA) is a term describing a group of immune-mediated rheumatologic diseases - the archetypical condition being ankylosing spondylitis (AS). The diseases predominately cause pain and stiffness of the spine, and can lead to spinal fusion. Although they can now be well managed, they are not curable - and since the usual age of onset is early adulthood, can be associated with a high burden of disease. Exercise has long been considered an essential ‘cornerstone’ of management, with general recommendations about regular exercise included in all recognised management guidelines. However, significant questions remain regarding specific exercise type, dosage and safety, and how exercise prescription should be tailored to the individual for optimal effect.

The first part of this thesis seeks to assess the current literature for exercise interventions in AS and provide guidance to health professionals, by the development of an evidence-based consensus statement. The process included systematic reviews, with meta-analysis where sufficient evidence was available, for the topics of: assessment; monitoring; safety; exercise type; physical activity; concurrent medications; setting and adherence. Specific recommendations were generated by an expert panel for each topic, and are presented as a framework which facilitates adjustment according to assessment findings, that is, an individually tailored approach.

A further knowledge gap is around the role of exercise designed to improve muscle fitness, that is, strength, power, endurance or motor control in axSpA. Early findings suggest there are pathophysiological changes in muscles with axSpA and the lumbar paraspinal muscles are almost always symptomatic. Therefore, more information about morphology and pathophysiological changes (such as inter-muscular adipose tissue (IMAT)) of these muscles could inform future exercise trial design. The second part of this thesis presents an exploratory pilot study investigating the size, symmetry and quality of the paraspinal muscles in a cross-sectional sample of people with axSpA. The most important finding from the magnetic resonance imaging (MRI) measures, was that there was significant fatty infiltration in both multifidus and erector spinae muscles, with a distribution that was largely symmetrical and most prominent at the lower lumbar levels. These findings support the need to investigate interventions targeting paraspinal muscle fitness.

In summary, the first set of evidence-based recommendations to guide exercise advice in AS, including important considerations such as safety, were developed. They are designed to be clinically useful, by incorporating a framework which can be adapted according to

individual needs. Information on morphometric muscle changes, and associated strengthening (resistance) exercise trials, are an identified knowledge gap. The pilot study findings of increased IMAT in a symmetrical distribution in the lower lumbar paraspinal muscles, may contribute to improved understanding of disease, and support the concept of evaluating an exercise program designed to improve paraspinal muscle fitness in axSpA.

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I would like to dedicate this thesis to the memory of my parents – to my dad, you taught us from an early age to love science (and that it is fun!) - and my mum, you never lost your curiosity or stopped asking questions.

Lastly, to my friends and family, most especially my husband Phil – it's been quite a journey… I thank you so much for your love and patience, and I look forward to having more time to spend with you – and the animals, food forest, walking boots and my bicycle.

Publication directly arising from the work described in this thesis

Chapter 3

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Oral Presentations

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'The lumbo-pelvic muscles and ankylosing spondylitis: an observational pilot study'

Australian Rheumatology Association Annual Scientific Meeting, Perth, Australia 2013
'Exercise for ankylosing spondylitis'

Australian Physiotherapy Association national conference, Brisbane 2013 (presentation made by Errol Lim)
'An Australian Consensus Statement: exercise for ankylosing spondylitis'

Australian Pain Society Annual Scientific Meeting, Hobart, April 2014
'Inflammatory Arthritis, Pain and Exercise: Where to begin?'

Australian Rheumatology Association Annual Scientific Meeting, Darwin, Australia 2016
'Sounds like a plan: exercise preparation for arthritis and pain'

Poster presentation

American College of Rheumatology Annual Scientific Meeting, San Diego, 2014
'Exercise for ankylosing spondylitis: it's still important'

Chapter 1: Introduction

‘Axial spondyloarthritis’ (AxSpA) is a chronic, incurable, painful and physically disabling condition that affects several million people worldwide. Since onset is typically in early adulthood, the personal lifetime burden of disease can be high. Traditional best practice management has included a combination of anti-inflammatory medication and exercise – both to be taken daily, for life. Recent advances in pharmacological management have improved outcomes for some people with axSpA; however, exercise is still considered a ‘first line’ management. Despite consistent recommendations for lifelong exercise, there are knowledge gaps regarding the best exercise choices to achieve the best outcomes. This project aims to consolidate the evidence, and thus optimise exercise advice, for people with axSpA.

1.1 What is axial spondyloarthritis?

Spondyloarthritis nomenclature

A group of immune-mediated arthritic diseases with a varied clinical phenotype are classified under the overarching term – ‘spondyloarthritis’ (SpA) – which is sub-divided into conditions affecting predominantly the peripheral (appendicular) and vertebral (axial) musculo-skeletal systems. These conditions are known as peripheral SpA (pSpA) and axial SpA (axSpA) respectively [1]. They share genetic and pathologic features, can be overlapping, and include psoriatic spondyloarthritis (PsSpA) and arthritis associated with inflammatory bowel disease, including Crohn’s disease [2].

Ankylosing spondylitis (AS) is considered the archetypical axSpA condition [3]. The name is derived from the Greek words ‘angkylos’ meaning bent and ‘spondylos’ meaning spinal vertebrae [4], referring to the end point of untreated disease, that is, a spine that is fused in a position of kyphotic (flexed forward) deformity. By definition (see Figure 1.1), a diagnosis of AS must include at least mild-moderate structural damage to the sacro-iliac joints – sufficient to be seen radiographically on X-ray.

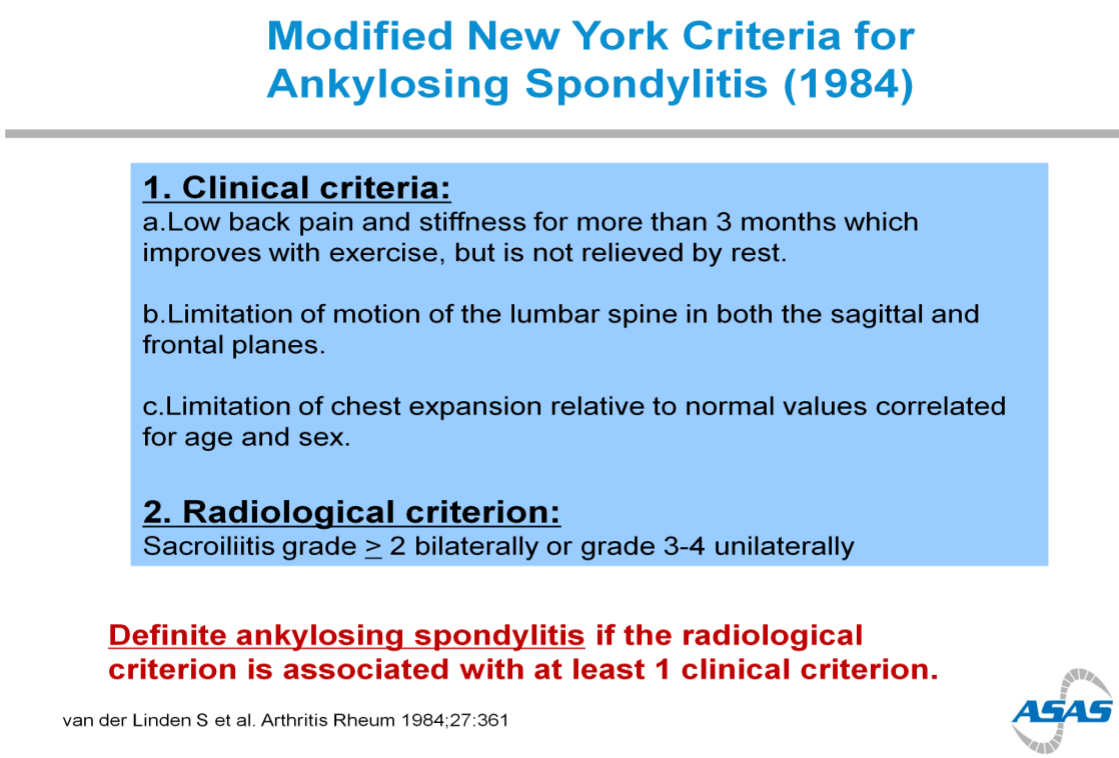


Figure 1.1 Assessment of SpondyloArthritis International Society (ASAS) criteria for Ankylosing Spondylitis.

ASAS slides downloaded from website (https://www.asas-group.org/) 01/09/2018: slides may be used freely therefore specific permission not required.

Increased knowledge over the last two decades led to the recognition of similar disease processes that are earlier or have less structural damage – hence the publication in 2009 of a new nomenclature and classification for the AS related conditions, as shown in figure 1.2 [5]. Within this classification, AS is considered a subset of the broader term ‘axSpA’, and can also be termed ‘radiographic axSpA’ – however, the AS ‘label’ remains in common use. Those who have similar clinical findings, but without at least moderate x-ray changes, are classified as having ‘non radiographic-axSpA’ (nr-axSpA). .

In this thesis, ‘AS’ is used in Chapter 3, since at the time of the literature search there were no published exercise studies using the ‘new’ nomenclature. However, the more modern term of ‘axSpA’ is predominantly used elsewhere

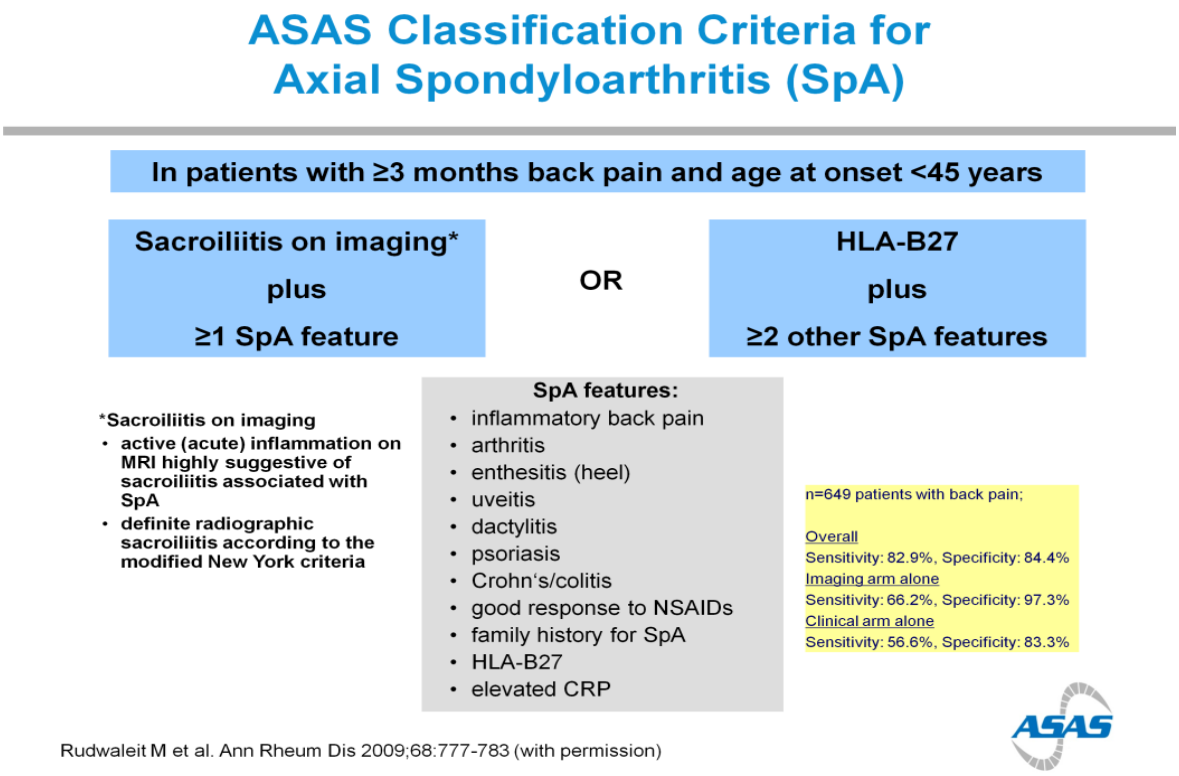


Figure 1.2 Assessment of SpondyloArthritis International Society (ASAS) criteria for axial spondyloarthritis. Source: ASAS educational slide

Epidemiology of axSpA

Due to its heritable preponderance (further described below), the prevalence of axSpA varies across racial groups from 0.5 to 1% for AS and up to 1.4% for axSpA [6-8]. Since Tasmania's population is largely of European origin [9], the population incidence is likely to be similar to that of Europe, that is, 0.54% – hence over 500 Tasmanians are likely to be affected by the condition. The incidence of axSpA in males and females is approximately equal, whilst more men than women are diagnosed with AS (that is, meet the radiographic criteria), in a ratio of 3.1:2 [10]. The usual age of onset is during early adulthood, usually in the third decade of life, although up to 20% may experience their first symptoms before the age of 20 [11]. Written descriptions of skeletons with ankylosed spines appeared from the 16th century onwards [12], however, ancient skeletons with fused spines, belonging to Egyptian pharaohs and medieval Anglo-Saxons [12], provide evidence that AS has been affecting humans for considerably longer.

AxSpA symptoms and signs

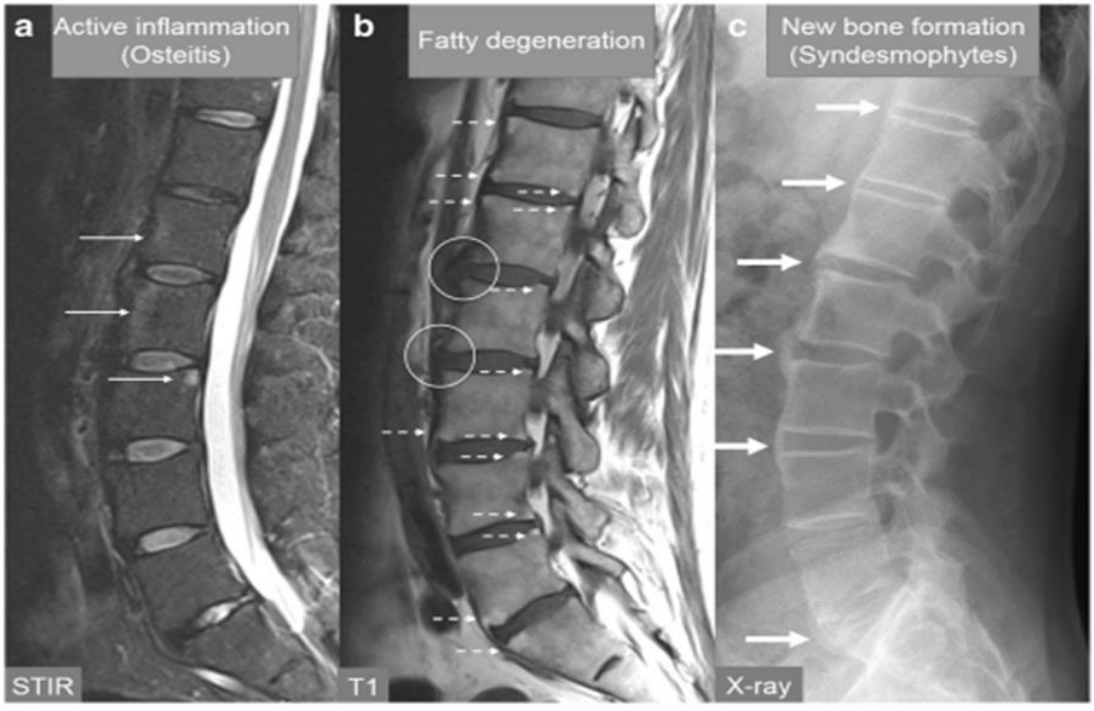
The cardinal symptoms of axSpA are spinal stiffness and inflammatory back pain, which is

further defined by the following criteria: spinal morning stiffness lasting more than 30 minutes; nocturnal pain, especially during the second half of the night; improvement with exercise and not rest, and chronic back pain (present for more than three months) with onset before the age of 45 years [13]. Other common manifestations are enthesitis, which presents as tenderness and inflammation at ligament or tendon insertions (such as the Achilles tendon), joint effusions producing swelling (usually lower limb, for example the hip or knee) and fatigue. Extra-articular manifestations of the condition can include uveitis, inflammatory bowel disease (including Crohn's) and psoriasis [7].

Aetiology and pathophysiology

The primary pathological change is enthesitis, that is, an inflammation at the anatomical region where ligaments, tendons or joint capsules attach to bone [3]. The enthesitis occurs at multiple sites and may be followed by osteitis, fatty degeneration of the adjacent bone marrow and secondary synovitis (Figure 1.3a,b)

Figure 1.3 Magnetic resonance imaging and X-ray of the lumbar spine showing structural (bony) progression in axSpA.



(a) osteitis, that is, active inflammation in the vertebral bodies; (b) fatty degeneration of the bone marrow (dotted arrows), that is, part of the repair process that leads to syndesmophyte formation, and (c) syndesmophytes, that is, osteoproliferative repair.

Adapted from Poddubnyy (2017) [14]. Permission granted by Springer Nature. 01/10/18; License Number 4440060734507

Disease localisation appears to be related to sites of higher biomechanical stress [6] – this includes the sacro-iliac joints in over 95% of cases. The subsequent healing process is thought to lead to exaggerated bone repair, resulting in the typical syndesmophyte formation, which can form a permanent 'bridge' over the joint space between one vertebra and another, as illustrated in figure 1.3c [14].

Without treatment, progressive disease will result in a gradual reduction in spinal mobility, frequently with an increasingly kyphosed (flexed forwards) posture, as shown in figure 1.4. If spinal ankylosis occurs, the affected joints of the spine will become permanently fused by bony bridging, and when the entire spine is affected, this results in 'total spinal ankylosis' (TSA): the spine effectively becomes one 'long bone'.

This is the spinal ankylosis typical of AS, and these bony/ structural changes can mark the evolution of the disease process from nr-axSpA into AS.

Figure 1.4 Person with advanced AS with total spinal ankylosis and severe thoracic kyphosis
Source: ASAS Educational Slide

In addition to significantly restricting mobility, people who have advanced axSpA are predisposed to a number of disease consequences, resulting in a significantly raised all-cause mortality rate, with a hazard ratio of 1.6 compared to the general population [15]. Increased cardio-vascular disease is thought to be the leading cause of death [16], however, osteoporosis

is the most common co-morbidity, it can occur within 10 years of symptom onset [17], and has a prevalence of over 50% [18, 19]. Due to the combination of osteoporosis and an ankylosed spine, there is an increased risk of both spinal fracture and associated spinal cord injury [20, 21]. Prevention of such disease sequelae by early diagnosis and optimal management is therefore paramount. However, as diagnosis is made by identification of a pattern of symptoms and signs, rather than one distinct or highly specific test, diagnostic delays remain common, and in Australia delays were found to be eight years on average [22].

Causes of axSpA

A number of predisposing associations with axSpA have been demonstrated, although their interactions and an exact pathophysiological sequence are not yet fully understood. Early descriptions recognised a familial component, and in 1973 an association with the human leucocyte antigen B27 (HLA-B27) was discovered [23]. The presence of HLA-B27 is thought to give an odds ratio for developing the disease of approximately 90, compared with those who are HLA-B27 negative [24]. However, since only about 5% of people with HLA-B27 develop axSpA, it is accepted that the disease results from one or more gene-environment interactions [25]. One environmental contributing factor is considered to be the microbiome, with an association between structural axSpA imaging findings, abnormal mucosal permeability and subclinical gastro-intestinal histopathology [26, 27]. Moreover, a recent theory proposes another possible environmental contribution, in the form of biomechanical stress – such as micro-trauma to the sacro-iliac joints [28-30]. Section 1.6 further describes the latter concept, which contributes to the rationale for the second phase of this thesis.

Diagnosis and assessment of axSpA

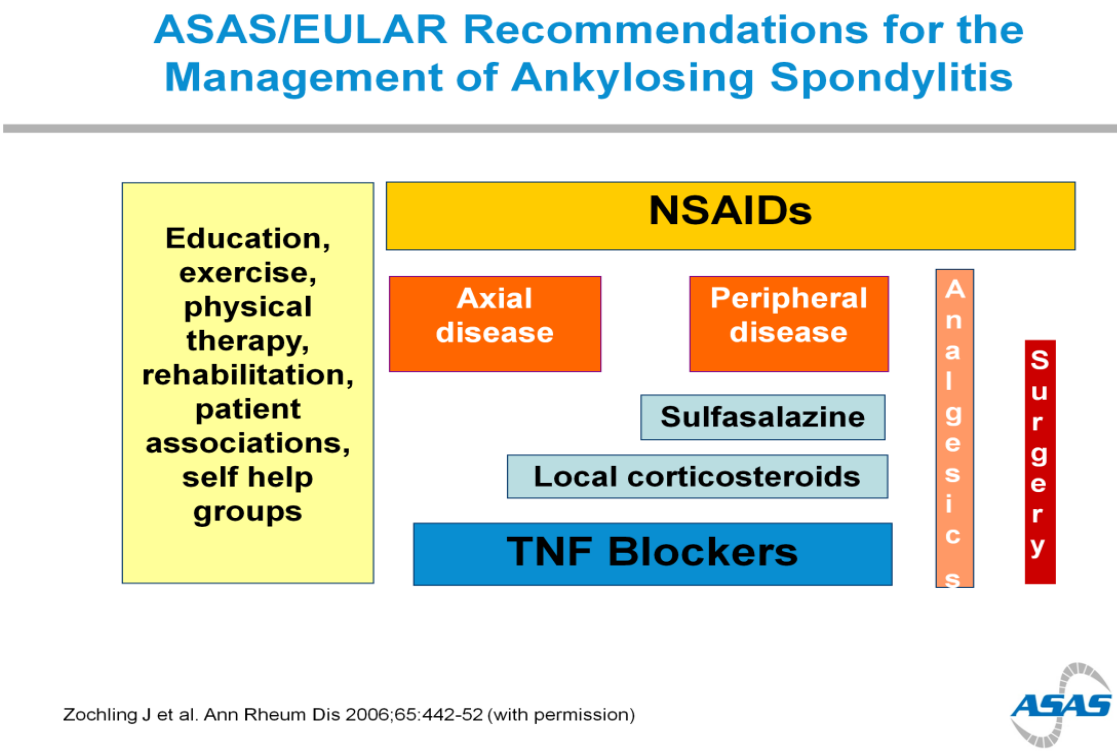
In clinical practice, diagnosis takes into account many facets of a patient's clinical findings, and the classification criteria may be interpreted more broadly for diagnostic purposes. For example, expert clinical reasoning would also include consideration of absent findings and other (perhaps more subtle) clinical signs [2]. Although radiographic sacroiliitis is a requirement for AS diagnosis, modern imaging assessment for axSpA diagnostic and monitoring purposes is usually by magnetic resonance imaging (MRI) [31]. Additional disease monitoring tools are inflammatory blood markers (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and a number of patient-reported outcome measures (PROMS) including the Bath AS Disease Activity Index (BASDAI) [32]. The most commonly used instrument for measuring axial mobility is the Bath AS Metrology Index (BASMI), which is a five-item index of spinal posture, lumbar spine flexion and lateral

flexion, cervical spine rotation and hip abduction [33].

1.2 Management of axSpA

Optimal axSpA management has long been established as comprising a combination of medical and non-medical management – the latter including education, exercise and other forms of physical therapy, rehabilitation and patient support groups , as illustrated in Figure 1.5.

Figure 1.5 Schematic diagram of the 2006 ASAS/ European League Against Rheumatism (EULAR) Guidelines for the Management of AS, indicating the long-established, relatively large contribution of exercise to AS management at all stages.
Source: ASAS educational slide



History of exercise and AS

Although there was some early recognition that exercise could be helpful [35, 36], during the second world war there was an imperative to enable young men in the British armed forces, who developed AS, to continue active service. More vigorous attempts at therapeutic exercise, that is, Army 'boot camp' style training, were found to be surprisingly effective [37]. These observations were later supported by case series studies of patients admitted to the Royal National Hospital for Rheumatic Diseases in Bath, England, and exercise was

established as an integral part of AS treatment. To this day, it is recommended as a first line management [38, 39], and throughout the disease course, as shown in Figure 1.5. Currently, there are over twenty randomised controlled trials (RCTs), and subsequent systematic reviews with meta-analysis [40, 41], which consistently demonstrate benefits for exercise programs across a range of parameters, as described in Chapter 3.

Note on terminology:

'Exercise' is defined as "the prescription of a physical activity program that involves the client undertaking voluntary muscle contraction and/or body movement with the aim of relieving symptoms or improving function, or improving, retaining or slowing deterioration of health" [42] and physical activity as "any bodily movement produced by skeletal muscles that expends energy" [43]. Since these terms are defined by context, rather than the physiological effect produced, they are used interchangeably throughout this thesis.

1.3 Why is optimal axSpA management (including exercise advice) important?

Despite all the treatment advances, the personal and socioeconomic burden of axSpA remains high, and exercise remains integral to optimal disease management. Additionally, there is now a compelling body of evidence that regular physical activity is essential for health, quality of life and longevity, yet people with autoimmune rheumatic conditions such as axSpA face additional challenges in achieving recommended exercise levels. These factors are explored further in the following section.

Medical management

During the 20th century, various pharmacological treatments (such as Phenylbutazone and steroid preparations) and non-pharmacological therapies (such as radiotherapy and plaster jacket immobilisation) were trialed, and largely discontinued due to significant adverse effects. A group of medications known as 'non-steroidal anti-inflammatory drugs' (NSAIDs) became available from the 1960s: these were better tolerated and moderately effective for most [7].

By the 1990s, more was known about the molecular and cellular pathology of axSpA and other types of inflammatory arthritis, allowing the development of a class of pharmacological treatments known as 'biologic disease modifying anti-rheumatic drugs' (bDMARDs), due to their capacity to down regulate specific antibodies and cells involved in autoimmune

inflammation [34]. The initial medications targeted tumour necrosis factor alpha (TNFα), a pro-inflammatory cytokine (cell signaling protein): and more recently other cytokines, such as Interleukin 17, have been targeted [2]. Taken together, the biologic medications have been a 'game changer', with most people experiencing a large and rapid reduction in symptoms and (most likely) prevention of progression of the disease [6].

Biological DMARDs have allowed rheumatologists to aim for low disease activity or remission of axSpA – such that some patients may experience few symptoms and have normal physical function. However, this is most readily achieved if treatment is commenced during early disease (the so called 'window of opportunity'), as if structural damage has already taken place, it cannot be reversed. Since the medications are expensive, people with axSpA have to meet specific criteria to receive subsidised medication, and the expected improvements are not universal. Therefore, the management of axSpA remains challenging, even with more effective medications.

Personal impact of axSpA

Due to the broad spectrum of disease severity, the personal impact of axSpA may vary from 'minimal' to 'devastating' [44]. Since the usual life stage of onset is early adulthood, the cumulative burden of symptoms (including pain, fatigue, stiffness and sleep disturbance) and signs (such as loss of joint range /mobility and spinal deformity) can be large, significantly impacting on life choices including occupation, leisure activities and personal relationships [45]. A reduction in quality of life (QoL) and physical function can precipitate psychological distress, which may be exacerbated by a delay in diagnosis [46].

A further source of psychological distress is progression to spinal ankylosis with a postural deformity, which can be associated with anxiety and depression [47]. Comorbidities are also more prevalent in advanced disease, and in a review of over 3000 people with SpA, 51% reported at least one comorbidity, and these were associated with poorer QoL, physical function and decreased employment [48]. Overall, around one third of people with axSpA cease work due to their condition, and 15% reduce or modify their employment: the personal financial cost, therefore, may also be high [45].

Lastly, translation of exercise recommendations into everyday life represents a time (and possibly financial) investment on the part of the individual concerned. A number of surveys have found variable adherence that appears likely to be similar to that of physical activity guidelines for the general population (Table 5, chapter 3) – in other words, at least one third

have very low levels of physical activity. A survey of 61 people with AS using the Exercise Benefits and Barriers scale [49] reported high scores for perceived barriers despite simultaneous high perceived benefits [50]. Thus, although many people with arthritis view exercise recommendations positively, for others the negative connotations of lifelong exercise represent an additional personal disease burden [51]. It therefore seems reasonable to ensure that only the most effective exercises are prescribed.

Socioeconomic costs

The direct healthcare costs associated with axSpA vary across countries, but have been shown to be 'high' [24], and, although annual costs are lower than for rheumatoid arthritis, the total cost is likely to be higher due to the lower mean age of onset [52]. In Australia, prescription of bDMARDs can only be made by a rheumatologist, and subsidy by the Pharmaceutical Benefits Scheme (PBS) under the National Health Act 1953 is restricted to adults with AS. It is likely that half to two-thirds of people with AS in Australia are managed long-term with bDMARDs [53], and the direct annual bDMARD costs range from $9516 to $14414 per person [54]. There are additional costs due to the PBS requirement of regular (six-monthly) rheumatologist monitoring for effectiveness. However, since in other countries, direct medical costs are estimated to represent only 23 to 50% of total annual costs for AS (due to loss of work productivity) [24], the total per person cost to Australian society is likely to be several tens of thousands of dollars each year.

Is exercise still important with biologic treatment?

With modern bDMARD management, there is an expectation that remission of the disease and maintenance of full axial mobility is achievable for some. Better symptom management may remove a 'prompt' for exercise therapy, and could call into question the need for exercise to remain as a first line management [55]. However, despite the goal of low disease activity or remission with these medications, axSpA is not yet curable. There is evidence that for some people, exercise levels may decline [56], and adipose tissue mass increase [57], following the onset of bDMARDs. Perhaps related to these findings, a number of studies (including high quality RCTs and a systematic review), have shown that exercise and bDMARDs are *synergistic* in their effect - that is, exercise adds significantly to a range of benefits (improved pain, mobility and disease activity) when people are already taking a bDMARD [58, 59]. Since costs for exercise interventions are perhaps one to five per cent of those for bDMARDs, cost effectiveness considerations alone support the ongoing inclusion of exercise as a primary management strategy.

‘Non-biologic’ disease management

People who have (structurally) milder disease may be well managed with exercise and NSAIDs, and never need bDMARDs – and/ or may not meet the criteria for their prescription. This applies to up to 40% of people with axSpA [60] – some of whom may simply not choose this treatment pathway due to safety concerns. Although bDMARDs have a good safety profile, they do result in immune system mediation (suppression) and are relatively contraindicated for people with a prior history of malignancy, demyelinating disease or tuberculosis [61]. Thus, there is always likely to be a group of people who remain more reliant on exercise for disease management, especially for control of pain and stiffness. Although the evidence has limitations, the effect sizes (ES) for exercise across a range of parameters can approach those seen for NSAIDs alone, and are discussed in detail in Chapter 3.

Symptom management

Significant proportions of people with axSpA experience ongoing symptoms, with mean pain ratings of 37/100 mm and 33/100 mm for spinal and spinal pain at night respectively, in a survey 333 people with axSpA: these scores were higher than for a comparison group with rheumatoid arthritis [62]. In addition, approximately two thirds of people with AS experience fatigue [47] and in a systematic review of 16 studies, reported depression ranging from 11 to 64%, with a pooled prevalence of 15% for at least moderate depression [63]. Associated sleep disturbance is also common, with a range of 35-90% reported in fifteen studies in one systematic review [64].

For some people, these symptoms remain, even when disease activity is considered to be at a low level, and/ or well controlled with a bDMARD. For example, fibromyalgia, defined as the clinical expression of central sensitisation, or ‘up regulation’ of pain, is common in concurrence with axSpA, with a prevalence of up to 25% [65]. Exercise is considered to play an important role in managing these symptoms in the general population [66, 67], and there are RCTs demonstrating improvement in related outcome measures in axSpA [68-70]. However, symptoms such as pain and fatigue can also be seen as a barrier to exercise in axSpA [71, 72], and there is evidence that exercise interventions with an inappropriate dosage may aggravate pain syndromes such as fibromyalgia [73]. Therefore, symptom management remains a key reason why exercise advice is important in axSpA – and particularly for those with persistent pain, fatigue, depression and/ or sleep disturbance, the *right* advice is likely to be a requisite for a successful outcome.

Disease modification and prevention of co-morbidities

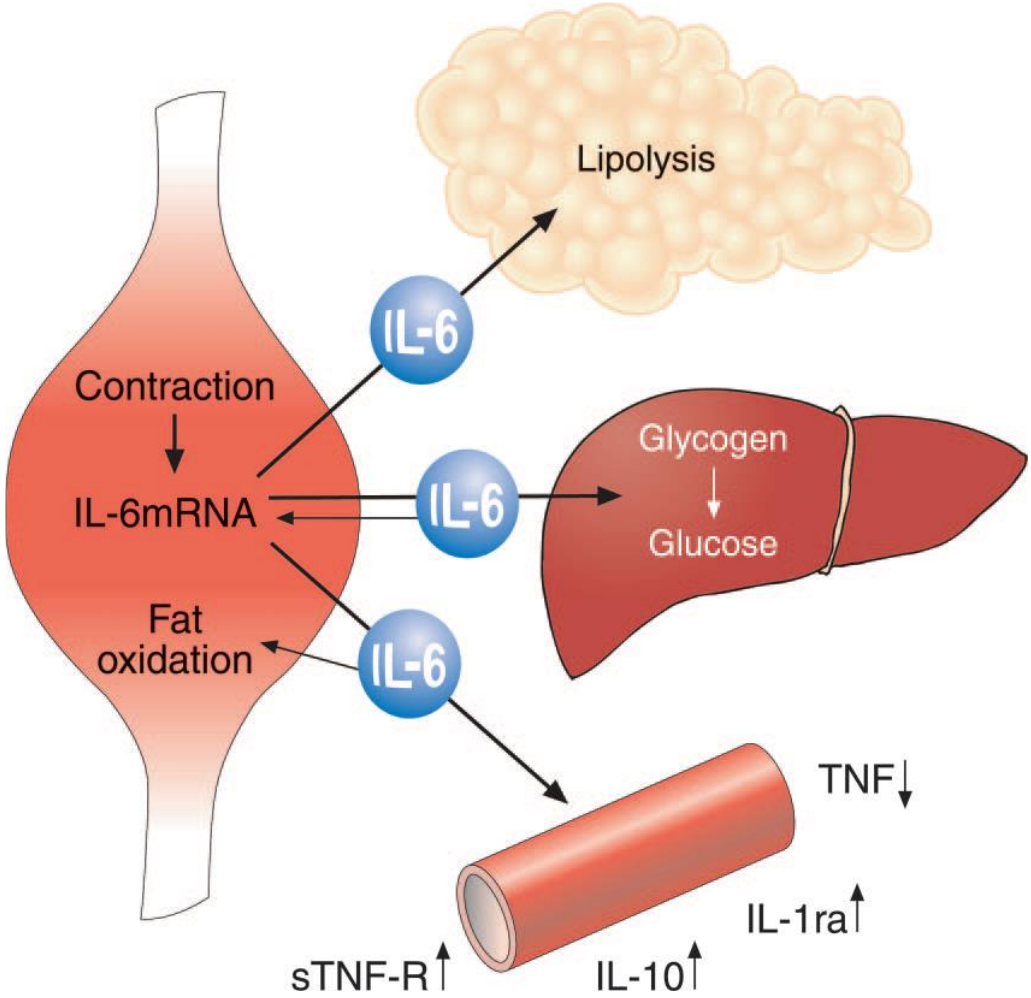
There are at least three postulated pathways in which exercise may modulate disease progression, and positively influence lifetime health:

Firstly, in clinical practice, people with axSpA can make at least short-term gains in mobility [74-77]. However, it is not known whether regularly repeated mobility exercises can prevent syndesmophyte formation, that is, the bony bridging of the vertebra, which can result in spinal fusion, by physically moving joints through their available range. Only three published RCTs have included long-term follow-up, with one suggesting some long-term (12 months) benefit for mobility [78], and two reports suggesting that gains in axial mobility can be maintained with sustained, long-term exercise practice [79, 80].

Secondly, bone density loss is a known consequence of axSpA [81, 82], and muscle strength/ mass have been shown to decline in some studies, as discussed in Chapter 4. It is not known whether strengthening exercises could prevent these changes. However, in other populations, specific exercise has been shown to significantly improve bone density [83] and can be targeted to preferentially strengthen sites vulnerable to fracture [84]. Since bDMARDs have not yet been shown to prevent osteoporosis in axSpA [85], exercise has a potentially useful role in maintaining bone health.

Lastly, there is now consistent evidence that exercise (in the right amount) can produce a net anti-inflammatory effect. In general populations, it has been recognised since the 1950s that, most people in industrialised countries need to deliberately exercise to be healthy [86]. Since then, there has been a large and compelling body of research to support this concept. Exercise acts by challenging homeostasis in all organ systems, activating acute & long-term adaptive mechanisms to preserve or re-establish homeostasis [87, 88]. At cellular level, this occurs via a complex combination of systems activation and crosstalk (Figure 1.6). Two main pathways are established: firstly, a reduction in visceral fat results in lower levels of circulating adipokines [89], that is, the pro-inflammatory cytokines released by adipose tissue, such as leptin and TNFα. Secondly, cytokines such as interleukin 6 (IL-6) are released by muscles on contraction [90]. It is hypothesised that IL-6 acts in a hormone-like manner to produce anti-inflammatory effects, such as increasing IL-10, whilst decreasing TNFα [91a]. It should be noted that, although IL-6 is generally classified as a pro-inflammatory cytokine, when muscle-derived it is involved in the anti-inflammatory effect of exercise [91b, 91c]. These findings have led Pedersen et al to propose that muscles are in fact endocrine organs, and that the cytokines released on muscle contraction should be known as ‘myokines.’ [92].

Figure 1.6 Anti-inflammatory effects (molecular response) of contracting skeletal muscle



The anti-inflammatory cytokine IL-6 is produced by skeletal muscle fibres and released on contraction. This induces metabolic effects such as lipolysis and fat oxidation, and has a role in glucose homeostasis during exercise. IL-6 has significant anti-inflammatory effects and may inhibit TNF-induced insulin resistance. Other net anti-inflammatory effects are produced by the down-regulation of TNF, and up-regulation of IL-6RNA, sTNF-R, IL-10 and IL-1ra.*IL-6 = interleukin 6; TNF = tumour necrosis factor; IL-6mRNA = IL-6 messenger ribonucleic acid; sTNF-R = soluble TNF receptor; IL-10 = interleukin 10, IL-1ra = interleukin 1 receptor agonist.*[88].

From Petersen et al (2005) **The anti-inflammatory effect of exercise.** Used with permission (granted 10/10/18) from the American Physiological Society.

Knowledge about the application of these effects in autoimmune rheumatic diseases remains patchy [93-95]. One recent example is the use of high intensity exercise for myositis: results from Swedish studies indicating that the effect was not only anti-inflammatory, but may also

modify genetic expression and therefore mediate disease progression [96]. A recent exploratory study investigating the effects of higher intensity exercise in axSpA also pointed to anti-inflammatory effects – including a reduction in BASDAI by an effect size of 1.4, which is greater than that for other AS exercise studies and within the range reported for bDMARDs [97]. Risk factors for cardiorespiratory conditions, such as arterial stiffness, also significantly improved and inflammatory markers remained stable, with a trend towards a decrease in IL-17 and IL-23.

Since inflammation is considered to be the unifying factor in many of the symptoms, consequences and comorbidities associated with axSpA, a reduction in lifetime inflammation may prove to be the most important reason of all to exercise regularly.

1.4 Limitations of the evidence regarding exercise and axSpA

Although clinical trials of exercise interventions for axSpA are now more numerous, significant knowledge gaps have been acknowledged in the literature [30, 55, 68], and remain problematic for both health professionals (HPs) involved in exercise prescription, and people who have axSpA. Due to the nature of the intervention, it is clearly difficult to avoid bias in exercise trials – for example, blinding of participants to the type of exercise in which they actively participate may not be possible. However, the level of evidence has improved from early non-controlled or blinded case series [98-100]: there is now an accumulation of over twenty RCTs: eighteen of which score six points or more on the Physiotherapy Evidence Database (PEDro) scale [101], indicating high internal trial validity.

Despite this trend towards better *methodological* validity, the following problems and knowledge gaps concerning *therapeutic* validity remain:

i. *Size of RCTs*. Table 1.1 presents the RCTs meeting the selection criteria for the study described in Chapter 3, with the addition of the RCTs that have been published since then – that is, all eligible exercise RCTs prior to 1st August 2018. Most exercise trials have small sample sizes: only 6 (30%) enrolled more than 25 participants in each group. This means that groups are usually not stratified – for example, by testing the effect of an intervention in early versus late stages of the condition, or active versus inactive, disease. This is important, since optimal exercise choices may be different for these groups, and hence the applicability of the intervention to clinical practice may be less clear.

ii. *Length of trial*. A lack of longer term studies investigating the effect of exercise (and evaluating the outcome if an exercise program is ceased) has also been recognised in the literature [102]. Most groups are followed for 12 weeks or less (15 or 75% of trials in Table 1.1). The short duration may mean that it is physiologically difficult for participants to attain optimal exercise benefits, particularly if they have commenced the intervention with a low level of baseline physical fitness, and the absence of good quality longitudinal studies means that it is not possible to evaluate the effects on disease progression.

iii. *Quality of exercise program design*. Problems with the design of exercise programs in trials led Hoogeboom et al to develop a measure for therapeutic validity: the Consensus on Therapeutic Exercise Training (CONTENT) scale [120]. This nine-point scale addresses aspects of exercise intervention such as participant selection; therapist competence; rationale for exercise content and dosage; intensity of intervention; appropriate monitoring, individual adjustment and adherence. Only nine studies (45%) assessed met the recommended cut-off score of six or more for therapeutic validity (Table 1.1). Furthermore, assessment of exercise associated physiological change (such as mobility, strength or cardiorespiratory function), was largely restricted to mobility (16, 80% of studies). Cardiorespiratory outcomes were measured in only 8 (40%) of trials, and none were identified that reported strength outcomes, despite evidence for reduced in strength in axSpA [121-124a].

iv. Lack of basic science to inform exercise program design - such as information about muscle pathophysiology in SpA. Historically, much more attention has been paid to SpA bony and entheseal changes than to the muscles themselves - despite long-held clinical beliefs about the effectiveness of exercise therapy. Physiotherapists and others have therefore empirically evolved and utilised muscle techniques, such as the principles of stretching (or lengthening) muscles that appear shortened, and re-training/ strengthening lengthened ones [74-78, 98]. These techniques could potentially be optimised for greater effect, if more was known about any underlying muscle pathophysiology. It also seems plausible that muscle changes may be more modifiable (with exercise) than bony changes. Lastly, identification of any loss of muscle mass or quality in middle age may allow targeted exercise interventions aimed at improving mobility in older age, with resultant positive effects on quality of life and mortality [124b].

In summary, although there have been improvements in the volume and methodological quality of exercise trials in axSpA, there appear to have been few attempts to trial novel exercise regimes which carefully consider exercise design and alignment with axSpA pathophysiology.

Table 1.1
Exercise for AxSpA: Randomised Controlled Trial Content, Quality and Therapeutic Validity

Study	Exercise Description	No in group	Duration (weeks)	Exercise type				PEDro Score /10	CONTENT score/9	Measure of relevant physiological change?
				Mobility	Strength	Cardio.	Unspec.			
Altan (2012) [103]	I: Pilates C: CE	30 25	12	X	X			8	4	Mobility only
Analay (2003) [104]	I: Supervised C: HEP	23 22	6	X	X	X		7	4	Mobility, cardio-resp
Cagliyan (2007) [105]	I: Supervised C: HEP	23 23	13 26	X	X			4	3	Mobility only
Demontis (2016) [106]	I: Multi-modal group exs & education C: Education only	20 22	8 8	√		X		6	6	Mobility only
Dragoi (2015) [107]	I: CE + respiratory muscle strengthening C: CE only	23 24	8	X	√*			7	7	Respiratory muscle function only
Dundar (2014) [108]	I: Aquatic exercise C: HEP	35 34	4	X	X	X		7	4	Mobility only
Fernandez-de-las-Penas (2005) [74]	I: Supervised GPR C: Supervised CE	20 20	6	√	X			6	7	Mobility only
Hidding (1993) [109]	I: Multi-modal group exs C: HEP	67 68	36	X	X	X		7	5	Mobility, cardio-resp
Hsieh (2014) [110]	I: Multi-modal HEP C: Mobility only HEP	9 10	12	√	√	√		7	6	Mobility, cardio-resp

Ince (2006) [75]	I:Multi-modal group exs C: Education only	15 15	12	√		√		7	5	Mobility, cardio-resp
Jennings (2015) [111]	I: Cardio + mobility C: Mobility only	35 35	12	√		X		8	6	Mobility, cardio-resp
Karahan (2016) [112]	I: Exergames C: No exercise	30 30	12				X	6	3	N
Kraag (1990) [76]	I: Home PT C: No exercise	22 26	16	√	X	X		8	5	Mobility only
Lee (2008) [113]	I: Supervised tai chi C: Tai chi HEP-video	13 17	8	X				6	3	N
Lim (2005) [114]	I: HEP C:No exercise	25 25	8	X				6	2	Mobility only
Maseiro (2011) [77]	I: Multi-modal group exs & education I: Education only C: No intervention	20 20 22	6	√		X		7	7	Mobility only
Neidermann (2013) [115]	I: Cardio + mobility exs C: Mobility exs only	53 53	12	√		√		8	8	Mobility, cardio-resp
Rosu (2014) [116]	I: McKenzie exs C: CE	24 24	24	√				5	4	Mobility, cardio-resp
So (2012) [117]	I: IS breathing exs + HEP C: HEP	23 23	16	X				6	6	Pulmonary function only
Sveaas (2014) [118]	I: Cardio + strength exs C: No intervention	10 14	12		√	√		7	9	Mobility, cardio-resp

√ = exercise program assessed as meeting American College of Sports Medicine (ACSM) guidelines for physiological effectiveness [119]; X = no evidence that exercise program met ASCM guidelines for physiological effectiveness; √* = inspiratory muscle strength training only; Home PT* Physiotherapy/ exercise delivered in participants' home, and customised to individual problem list; I intervention group; C control group; CE conventional exercises; HEP home exercise program; 'multi-modal' = components of three or more exercise types, that is, mobility, strength, cardio-pulmonary; GPR global postural re-education exercises; IS incentive spirometer; Mobility = mobility exercise (includes stretching); Strength = strengthening (resistance) exercise; Cardio. = cardio-pulmonary (aerobic) exercise; Unspec. = exercise type not specified; PEDro score = Physiotherapy Evidence Database scale for internal validity; CONTENT = Consensus on Therapeutic Exercise Training scale for therapeutic validity of exercise programs.

Issues for patients and HPs

In practical terms, the evidence gaps described make the interpretation and translation of the available evidence problematic – for both people with axSpA and HPs with the role of providing exercise guidance. Typical pragmatic questions from the latter group were collated in the initial stages of the Consensus Statement (CS) project (chapter 3), and are listed in as supplementary appendix B. Given that these questions were generated by a group of physiotherapists experienced in providing advice to people with axSpA, it can be seen that 'real-life' implementation of exercise advice can be problematic – and presumably is more so for those HPs with less knowledge or experience.

For people with the condition, there are now excellent resources that include detailed instruction on a wide variety of exercises, such as the United Kingdom's National Ankylosing Spondylitis Society's web-based videos and mobile device 'apps' [125]. However, it is difficult for such resources to address issues around actual exercise choice for optimum effect, due to the wide spectrum of axSpA expression and severity, and the countless possible variations in exercise indications and performance. For those people with an ankylosed spine, the increased risk of falls [126-128] and subsequent spinal fracture/ spinal cord injury [20, 129, 130] are significant safety issues that clearly require consideration.

The identified evidence gaps around exercise dosage can also impact on both short-term implementation of regular exercise programs ("where to begin") and sustainability. One of the most significant barriers may be fear of causing a flare-up – either of pain, or of inflammation/ the disease itself , with a cross-sectional study concluding that a large proportion (78%) of 148 people with AS experienced barriers to physical exercise, and these were mostly disease related – for example, pain, stiffness, fatigue and disability [72].

Lastly, the introduction of bDMARD medication has led some to question the necessity of exercise in the management of axSpA [55, 131, 132]. *The objectives of the project described in Chapter 3: 'Exercise for ankylosing spondylitis: an evidence based consensus statement' were therefore to analyse the existing evidence, apply an expert consensus process to interpretation of the evidence, and develop more specific recommendations to guide sustainable exercise advice.*

1.5 Strength and stability in axSpA

Exercises that aim to enhance aspects of muscle fitness, that is, strength, endurance, motor control and power, broadly fit under the umbrella term of 'strength' or 'resistance' training, and are recommended by the ACSM and in national physical activity guidelines for adults of all ages [43, 119]. Muscle size and quality, measured by imaging, histopathological examination and body composition measures, are accepted surrogate markers for muscle function [133-135]. Although there are some conflicting findings, which are discussed in Chapter 5, it is recognised that there can be pathophysiological changes in the muscles of people with axSpA [136-138] – resulting in loss of both axial and appendicular strength. There is little information to indicate whether such changes are primary, that is, as a result of inflammatory intra-muscle processes, or secondary - that is, consequential to disease signs or symptoms.

Given these findings, there is a surprising paucity of evidence to investigate the effect of resistance exercise aimed at improving muscle fitness in people who have axSpA. Although a number of exercise trials stated that they included performance of strength exercise, only six could be identified that met the ACSM criteria for physiological effectiveness - that is at least 8–12 repetitions of each exercise, with resistance such that fatigue is reached, performed two-three times per week. In these studies, exercises were described that were adequate for producing a change in strength, but the effects of the exercise programs adopted on either axial or appendicular strength were not reported (Table 1.1). No axSpA studies were identified that aimed to assess or improve other aspects of muscle function, such as motor control, endurance or power, or that specifically targeted improvement in paraspinal muscle function.

1.6 Rationale for investigating the paraspinal muscles

Given that the cardinal symptom in axSpA is painful low back stiffness, commonly described as lumbar region 'muscle soreness', the paraspinal muscles would appear to be an obvious target for further investigation. The relevant functional anatomy and how it may relate to the disease is further discussed in the following section.

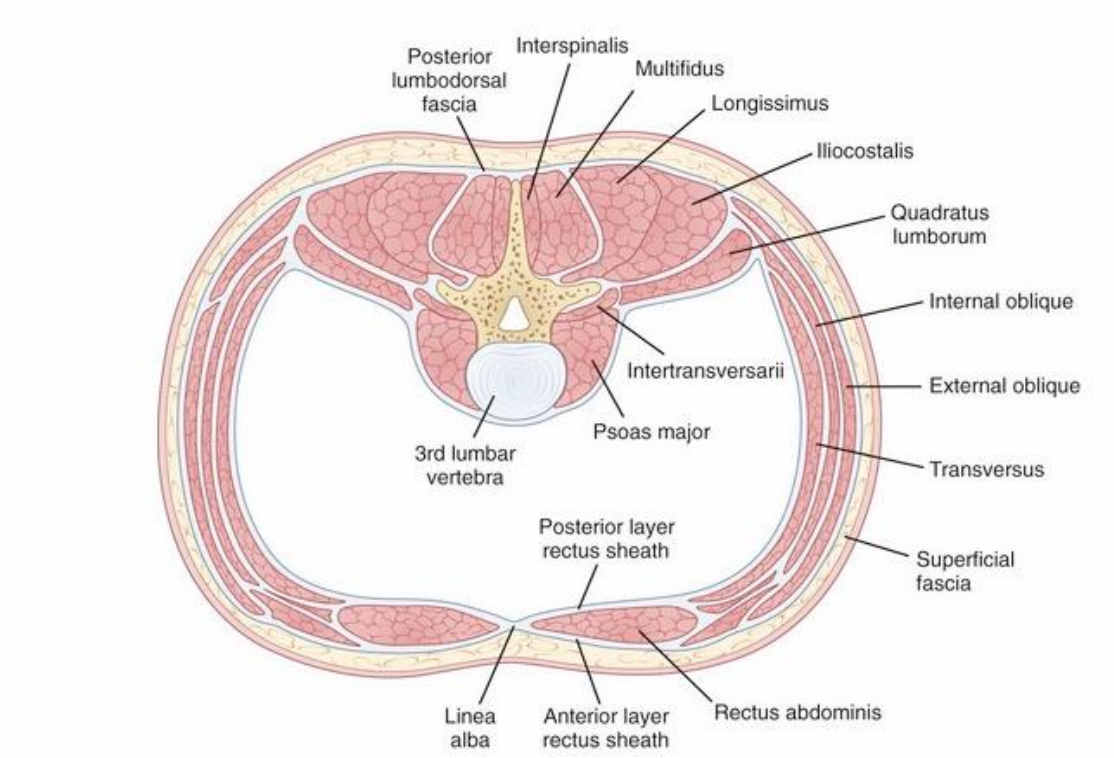
Lumbar paraspinal muscles

The term ‘paraspinal muscles’ encompasses the complex group of strap-like muscles which lie adjacent (lateral) to the posterior mid-line formed by the spinous processes, and posterior to the plane of the transverse processes of the vertebral bodies (Figure 1.7) [139].

The muscles thus lie in a largely vertical plane from pelvis to skull. The lumbar paraspinal muscles are defined as those that exert action on the lumbar spine [140], and can be considered as two main groups:

- The lumbar multifidus (LM) is the most medial muscle (figure 1.7) and comprises a series of overlapping fascicles – the deepest (intersegmental) fascicles spanning between two vertebrae only, and the more superficial fascicles spanning two or more joints. The whole forms a fan shape over the lumbo-pelvic region, arranged so that the posterior aspect of each lumbar vertebra has muscle fascicles radiating to each vertebra below it, and to the sacrum and iliac crest [140]. This structure thus reflects the key function of LM as a dynamic spinal stabiliser, providing continuous small adjustments to counteract the forces of gravity, movement and loading, and thus maintain vertebral alignment and stability [139, 140]. Anatomically the most stable position for the lumbar spine is the lordotic curve [141]: each fascicle of LM is therefore considered to control the lumbar lordosis at its particular spinal segmental level.

Figure 1.7 Cross section of body musculature and fascia through L3 showing intrinsic spinal musculature.



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https://musculoskeletalkey.com/lumbar-musculature-anatomy-and-function/

- The lumbar erector spinae (LES) comprises of the lumbar sections of the longissimus and iliocostalis muscles. The lumbar longissimus lies lateral to the LM muscle and is made up of five fascicles: each one originates from the transverse process of a lumbar vertebra and inserts caudally into the erector spinae aponeurosis [142]. The latter is a sheet of tendinous fibres that attach onto the sacrum and ilium, to form a common attachment for the LES muscles. The iliocostalis is a more superficial muscle: its fascicles originate from the lower posterior rib cage, and attach to the ilium via the LES aponeurosis, with no direct attachment to the lumbar spine [139]. Both LES muscles control forward lumbar flexion by eccentrically controlling the rotation (in conjunction with the MF muscle) and anterior translation of one vertebra upon another, and are highly active during spinal extension from a flexed position [140].

Why investigate the lumbar paraspinal muscles in axSpA?

As discussed in section 6 of this chapter, there are important evidence gaps regarding exercise that targets muscle fitness parameters in axSpA – and in addition, there is a limited amount of information regarding paraspinal muscles in the condition. A previous MRI study provided absolute values for individual muscle total cross-sectional area (CSA) and grading of muscle quality (fat infiltration) using a three-point scale, at the L2 to L5 vertebral levels. Comparison (without further analysis) was made between a group of 22 participants with radiographic axSpA (AS) with 14 participants with non-radiographic axSpA (nr-axSpA) and it was concluded that the AS participants had higher levels of inter-muscular adipose tissue (IMAT) than those with nr-SpA [136]. Bok et al measured total paraspinal muscle CSA on MRI at the L4/5 vertebral level only, comparing 31 males with AS with 31 control participants with LBP, matched for age and spinopelvic alignment, and a further group of 20 males with AS and spinal deformity (for whom matched controls could not be found). This measure of a paraspinal muscles at a single vertebral level was significantly smaller in the AS group with spinal deformity, compared with the AS group – and the latter was significantly smaller than controls [137]. Lastly, a recent MRI study assessed the total CSA and graded fatty infiltration of the combined paraspinal muscles from L1/2 to L4/5 vertebral levels for 51 participants with AS and 51 control participants matched for age and sex. Comparison between the two groups revealed smaller total CSAs in the AS group at each level [138]. No studies were found that examined the L5/S1 vertebral level, despite its close proximity to the SI joints and important biomechanical role.

Therefore, further investigation, including separate measures for each of the paraspinal muscles, at multiple spinal levels (including L5/S1), and analysis of symmetry and muscle quality, with adjustment for the known confounders of age and sex, appears warranted. The following rationales are also submitted in support of further study:

i. Disease understanding. As previously discussed, the most common region for inflammatory change in axSpA is the lumbo-pelvic region – that is, the sacro-iliac joints and lumbar spine, and the primary tissue target is the enthesis. However, it is not known whether the local inflammatory environment produces either primary or secondary change within the anatomically adjacent muscles. Should a pathophysiological change be identified, it may explain why axSpA symptoms

typically ease with exercise and become worse with rest or static postures – the latter commonly described as ‘muscle stiffness’ [143].

ii. Better exercise advice. Identified changes in the size, symmetry or quality of the paraspinal muscles may indicate a target for trials of novel exercise programs, such as those that aim to re-educate motor control of these particular muscles, functional stability, strength and endurance. Such programs have been demonstrated to be effective in appropriately selected groups with ‘non-inflammatory’ low back pain (LBP) [144].

iii. Improved function. The lumbar paraspinal muscles have separate but overlapping and coordinated roles in maintaining the lumbar lordosis, that is, the neutral and anatomically stable postural curve of the lumbar spine that is integral to normal spinal function [145, 146]. Since loss of the lumbar lordosis (flattening of the lumbar spine) is a typical consequence of axSpA progression, it seems plausible that specific exercise programs aiming to maintain the lordosis could be beneficial. An additional reason to examine the concept of paraspinal muscle involvement in axSpA is the role played by the LM muscle in spinal proprioception and balance [147-149]: again balance is known to be decreased [127, 150, 151] and there is an increased risk of falls [129, 130, 152] in some people with axSpA.

iv. Relationships with general health. There has been a growing increase in recognition of the role of muscles in maintaining general health, due to their role in managing metabolic inflammation, as discussed in section 1.3. Diminished muscle quality, as determined by the presence of ectopic adipose tissue (inter-muscular adipose tissue (IMAT)) is also known to be positively associated with insulin resistance, hypercholesterolaemia and strength and mobility impairment [153].

v. Causative factors. Biomechanical strain is postulated to be a causative factor for axSpA: increased tone in the paraspinal muscles has been hypothesised to increase lumbo-pelvic compressive forces [143, 154], with such strain producing microtrauma which triggers or maintains local enthesitis [30, 155, 156]. An alternative cause of biomechanical strain could be muscle asymmetry – which has been shown to be associated with LBP [157, 158]. The biomechanical hypothesis in axSpA is based upon the results of a transgenic mouse model study, where spinal traction (decreased

force across the spinal joints) was found to prevent joint ankylosis, and weight bearing (increased force) to be associated with ankylosis [29, 159]. The finding has resulted in questions in the literature arising with respect to the potential for exercise to add to disease progression [30, 155, 156, 160]. However, given that:

(a) the lumbar paraspinal muscles play an essential role in the performance of upright (anti-gravity) physical activity and maintenance of optimal spinal posture, inter-segmental stability and balance [140, 161, 162];

(b) LM and LES have different primary functions (as described above), and,

(c) there are a multitude of compelling reasons in favour of exercise targeting general muscle fitness [153, 163], further information on axSpA muscle changes and complementary exercises would seem imperative.

vi. Lastly, evidence of axSpA conditions was historically based on x-ray (and thus bony) changes and that emphasis continues to this day. Any identified between group differences (AS/axSpA and healthy controls) in imaged appearance of the paraspinal muscles may make a useful contribution to diagnosis and therapeutic monitoring and evaluation.

Chapter 5 describes a pilot study to examine the size, symmetry and quality of the LM and LES muscles seperately at multiple lumbar vertebral levels, in order to inform future research directions including exercise prescription aimed at targeting specific aspects of muscle fitness in axSpA.

1.7 Summary

Axial spondyloarthritis is an auto-immune rheumatic disease that predominantly affects the spine, but is associated with a high incidence of systemic co-morbidities. The disease ‘end point’ is total fusion of the spine, and this circumstance is associated with significantly increased morbidity and mortality. Contemporary management aims to prevent such structural progression - however, the effective disease modifying medications are costly and their subsidised use is restricted to those people demonstrating specific criteria for disease activity and structural progression. Exercise is a long established, integral

component of management, and regular exercise - for life - is recommended in all axial spondyloarthritis guidelines. Despite this, and the extensive amount of evidence for the necessity of exercise to maintain health in the general population, substantial knowledge gaps remain. There is a lack of detail about how exercise may interact with the pathophysiology of axial spondyloarthritis [160], and consequently, exercise advice lacks essential components such as the optimal type, dosage and frequency of exercise, and how it may be adapted to accommodate different disease stages and presentations. And, despite early evidence of decreased muscle strength and pathophysiological changes, there is negligible information to inform exercise that targets muscle fitness in axSpA.

1.8 Structure of this thesis

Chapter 2: Research Aims. This chapter briefly describes the aims of two studies: 'Exercise for ankylosing spondylitis: an evidence-based consensus statement', and 'Size, quality and symmetry of the lumbar paraspinal muscles in axial spondyloarthritis'.

Chapter 3: Exercise for ankylosing spondylitis: an evidence-based consensus statement. This chapter presents the results of a systematic review with meta-analysis. It identifies key evidence gaps and develops an exercise framework and evidence-based recommendations, targeting health professionals who work with people who have ankylosing spondylitis. The text of this chapter has been published [69].

Chapter 4: Research Methods. This chapter describes the axSpA assessment measures utilised for the study presented in the following chapter.

Chapter 5: Size, symmetry and q*uality of lumbar paraspinal muscles in axial spondyloarthritis.* This chapter reports morphometric measures of the lumbar paraspinal muscles, and their association with sex, age and body mass index, at multiple lumbar levels in a cross-sectional sample of people with axSpA.

Chapter 6: Summary. This chapter summarises the findings and conclusions of the thesis.

Chapter 7: Future directions. This chapter suggests directions for future research.

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Chapter 2: Research Aims

The aim of this thesis is to consolidate the evidence for advice provided to people with axSpA: firstly, by improving the specificity of exercise recommendations, and secondly by describing the lumbar paraspinal muscles, in order to inform future directions for research into developing optimal axSpA exercise programs.

2.1 Exercise for ankylosing spondylitis – an evidence-based consensus statement

The primary aim of this study was to develop specific recommendations, based on the best available level of evidence and expert consensus opinion, by addressing the following questions in adults with AS:

- Which measures are beneficial for baseline mobility assessment, in order to inform exercise prescription?
- What are the minimum requirements for monitoring these measures?
- What safety aspects should be considered in relation to exercise prescription?
- Is exercise effective for disease modification, compared with no exercise?
- Are exercises in combination with a biologic medication more beneficial, for pain, function, disease activity and mobility, than medication alone?
- Is therapeutic (specifically prescribed) exercise aimed at: (a) improving mobility and posture; (b) increasing strength; (c) improving cardiorespiratory fitness, and (d) improving function (balance, co-ordination, gait, agility and proprioception) more beneficial for pain, mobility, disease activity and physical function than no exercise or general physical activity advice only?
- What types of physical activity are beneficial for pain, mobility, disease activity and function, compared with no physical activity?
- What volume of exercise is best for pain, mobility, disease activity and function?
- Which factors are beneficial for supporting adherence to an exercise plan?
- Which exercise setting is most beneficial for pain, function, disease activity and mobility?

The secondary aim of the study was to identify the evidence gaps in exercise for AS, in order to provide indicators for future research pathways.

2.2 Size, symmetry and quality of the lumbar paraspinal muscles in people with axial spondyloarthritis

This exploratory pilot study aimed to describe the size, symmetry and quality of the lumbar paraspinal muscles (multifidus and the lumbar erector spinae group) in a sample of people with axSpA, and examine associations of muscle measures with age, sex and body mass index.

Chapter 3: Exercise for ankylosing spondylitis: an evidence-based consensus statement

Preface

This chapter describes the work of a national expert panel, comprising a rheumatologist and ten physiotherapists with experience in the treatment of AS, who represented all Australian states and the territories (except the Australian Capital Territory). The physiotherapists were members of a special interest group of the Australian Rheumatology Health Professionals Association. The submitter of this thesis was the lead author for the paper and supplementary appendices, and also: led the planning of the project; coordinated and collated the independently-generated clinical questions; performed the systematic reviews; developed the literature review tools; distributed papers for review by team members and collated the results; developed the exercise framework and generated and implemented surveys of HPs and people with axSpA to test the importance of the recommendations. Dr Zochling chaired and coordinated the two day face to face meeting of the panel members, which resulted in the exercise recommendations.

This text of this chapter has been published [1].

The paper has now been cited in almost 40 other publications, the most important of these being:

i. *Therapeutic guidelines: Rheumatology Version 3 2017 Rheumatology Expert Group.*
ISBN 978-0-9804764-8-4. Melbourne, Therapeutic Guidelines Limited

The recommendations presented in this chapter are cited as the guide for further information about exercise in axSpA in the latest edition of this well regarded guideline, which is also available as an electronic version.

ii. *Hinze AM, Louie GH. Osteoporosis Management in Ankylosing Spondylitis. Current treatment options in rheumatology. 2016 Dec 1;2(4):271-82.*

This guideline for osteoporosis management in AS cites the information found on exercise safety in this chapter.

iii. *Debusschere K, Cambré I, Gracey E, Elewaut D. Born to run: The paradox of biomechanical force in spondyloarthritis from an evolutionary perspective. Best Practice & Research Clinical Rheumatology. 2018 Sep 1.*

This recent review discusses the evidence for a biomechanical component to axSpA pathogenesis, citing the paper presented in this chapter as evidence in support of exercise.

iv. *Robinson Y, Olerud C, Willander J. Do biological disease-modifying antirheumatic drugs reduce the spinal fracture risk related to ankylosing spondylitis? A longitudinal multiregistry matched cohort study. BMJ open. 2017 Dec 1;7(12)*

A conclusion of this investigation cited the paper in this chapter as follows: "therefore, recommendations for physiotherapeutic guidance for spinal injury prevention are valid even for patients receiving bDMARD".

The exercise framework presented at Figure 1 has been recommended to members of the Spondylitis Society of America, and the plain language version of the recommendations translated into German by a patient support group. Material from the paper also formed the basis for the following presentations at national conferences:

- 'Exercise for ankylosing spondylitis' - oral presentation selected following abstract submission to the Australian Rheumatology Association Annual Scientific Meeting, Perth, Australia May 2013
- 'An Australian Consensus Statement: exercise for ankylosing spondylitis' – oral presentation selected following abstract submission to the Australian Physiotherapy Association national conference, October 2013 (presentation made by Errol Lim)
- 'Exercise for ankylosing spondylitis: it's still important' – poster selected for presentation following abstract submission to the American College of Rheumatology Annual Scientific Meeting, San Diego, October 2014
- 'Inflammatory Arthritis, Pain and Exercise: Where to begin?' oral presentation (invited speaker) at the Australian Pain Society Annual Scientific Meeting, Hobart, April 2014
- 'Sounds like a plan: exercise preparation for arthritis and pain' oral presentation (invited speaker) at the Australian Rheumatology Association Annual Scientific Meeting, Darwin, Australia May 2016

3.1 Abstract

Objective

Despite Level 1b evidence and international consensus that exercise is beneficial in ankylosing spondylitis (AS), there is a paucity of detailed information to guide exercise prescription, including the type and dosage of exercise required for the most benefit. This collaborative project, combining evidence with clinical expertise, was established to develop practical recommendations to guide sustainable exercise prescription for individuals with AS.

Methods

Using a modified Delphi technique, 10 clinical questions were generated and a systematic literature review was conducted for each. Draft recommendations were developed at a 2-day meeting, based on the integration of evidence summaries and expert opinion. Feedback was obtained from patient and health professional groups prior to finalisation.

Results

Recommendations and practice points were developed for the following areas: assessment; monitoring; safety; disease management; AS-specific exercise; physical activity; dosage, adherence and setting. A framework was developed that could also be adapted for exercise in other chronic musculoskeletal conditions. Feedback suggests that the final consensus statement provides useful information for those seeking to provide best practice exercise prescription for people with AS.

Conclusion

The recommendations provide an up-to-date, evidence-based approach to the full range of issues related to the use of exercise in AS, as well as identifying evidence gaps for further research. Most importantly, this includes investigation of aspects of exercise programme design required to produce the largest effect, long-term adherence with exercise programs and the specific exercise requirements of sub-groups of people with AS. Widespread dissemination and implementation of the guidelines will be required to optimise exercise outcomes.

3.2 Introduction

Individuals with ankylosing spondylitis (AS) experience pain and stiffness, which mainly affects the axial skeleton (spine, hips and shoulders). Since the condition is an inflammatory arthritis, fatigue can also be a prominent symptom [1]. The primary pathology includes enthesitis, or inflammation of the anatomical region of the bony attachment of tendons, ligaments or joint capsules [2]. Typically this occurs in the spine; if unchecked, new bone formation may result in ankylosis, or spinal fusion. The most common age of onset is in early adulthood, therefore the lifetime individual impact of AS can be high [3]. Traditionally, the condition has been managed with a combination of anti-inflammatory medication and exercise, with the latter appearing anecdotally to be more effective than for other types of arthritis.

Although exercise recommendations feature prominently in relevant clinical guidelines for the management of ankylosing spondylitis [4, 5, 6, 7], and are supported by a body of mixed-quality evidence [8], in clinical practice there is a lack of specific information to guide exercise planning [9, 10]. The majority of published evidence focuses on mobility exercise [9], and relatively little attention has been given to other aspects of exercise program design such as strengthening, balance or cardiovascular exercise, despite recognition that AS can affect muscle strength [11], balance [12] and cardiopulmonary function [13]. Similarly, there is little information about dosage (frequency, intensity and duration) or adherence to recommended programs [9]. Several trials are based on intensive, time-limited (often residential) exercise modalities which are not readily available in many regions - such as in-patient rehabilitation or spa therapy/ exercise combinations [14]. Lastly, recent rapid advances in medical management, such as tighter control of disease activity by the use of anti-tumour necrosis alpha (anti-TNFα) factor agents, have raised questions about the ongoing relevance of exercise in the management of AS [15].

The task of developing an optimally effective, evidence based and sustainable exercise program for a person or a group with AS therefore remains challenging. The overall objective of this project was to develop more specific recommendations covering a range of topics which need to be considered for exercise prescription - primarily for use by health professionals, but also for people with AS who may wish to acquire more detailed information about the use of exercise as a self-management strategy.

3.3 Methods

Systematic review

The Writing Group (WG) comprised eleven physiotherapist members of an ankylosing spondylitis special interest group in Australia, and a rheumatologist (JZ) with experience in Delphi methodology and guideline development. WG members independently submitted up to ten questions of clinical importance to their practice, which were grouped into nine topics by the project coordinators (JM and JZ). These were: Assessment, Monitoring, Safety, Disease Management, AS-Specific Exercise, Physical Activity, Dosage, Adherence and Setting. A systematic review was carried out for each topic: details of the methods are shown in Appendix A (section A1). All WG members then participated in the assessment of included studies, using a pro forma 'article summary' tool to record quality, relevance to a non-residential setting and reproducibility of the exercises in a 'real-life' context. Meta-analysis was performed using random effects models where data was available to allow pooling – that is, for pain, disease activity, spinal mobility measures (cervical mobility, fingertip to floor distance, chest expansion and lumbar flexion) and physical function. An 'evidence matrix' was compiled by the coordinators to show: the number, type and quality of studies; overall level of evidence; consistency of results, and, (where applicable) effect sizes. Any discrepancies were resolved by discussion. Details of the flow of studies are shown in Figure A1, included and excluded full text papers (with reasons for exclusion) at A2 and A3 and evidence for the recommendations at Appendix B.

Consensus Meeting

A two day face-to face meeting was held to review the evidence and develop recommendations, during which WG members presented topic summaries, as described above. These findings were discussed in the context of the collective clinical experience of the group, before recommendations were derived for each topic. After gaining appropriate ethics approval, consumer and health professional feedback on the draft recommendations was obtained by anonymously surveying people with AS (via patient support groups) and health professionals (via professional organisations). Further information regarding the surveys is provided in Appendix C, section 1 (C1). The consensus statement wording was adjusted and further independent voting by the WG was used to finalise each recommendation.

Grade of Recommendations

The Australian National Health and Medical Research Council (NHMRC) hierarchy [16] was used to grade the recommendations as follows: ***Evidence Based Recommendation (EBR)*** Based on a body of evidence, graded A-D depending on types of studies and consistency of results; ***Consensus Based Recommendation (CBR)*** developed by the WG in the absence of direct evidence, or poor quality evidence, to answer the question, and **Practice Points (PP)** developed by the WG where there was a need to provide practical guidance to support the implementation of EBRs and CBRs. The derivation of PPs is shown in Appendix C, section 2 (C2).

3.4 Results

The final ten recommendations with practice points are listed at Box 1. The process of developing the recommendations highlighted the complexities of therapeutic exercise prescription and the potential for multiple interactions between the different topics examined. Figure 1 summarises the recommendations and relationships of these factors, and may be useful in informing joint (patient and health professional) decision making regarding exercise choice. A plain language summary of the recommendations and framework is also provided in Appendix C, section 3 (C3). Survey results (Table C1) demonstrated a high level of patient importance (mean for all recommendations 8.46/10; range 8.0 to 8.9) and health professional (HP) support (mean 8.66 and range 7.3 to 9.58). The mean proportion of HPs who stated that the recommendation was already their practice was 60.2%, whilst 21% stated that the recommendation would modify their practice. 0.8% of HPs reported that they did not wish to change their practice, and the remainder (17.8%) stated that the recommendation did not apply to their practice. The background, clinical question(s), results and rationale for each recommendation are outlined as follows:

Assessment and Monitoring

Background

Pre-exercise objective physical measures are an established component of individual exercise prescription, serving to inform: individual training goals; appropriate exercise type(s); starting dose precautions (which may indicate exercise modification), and personal information regarding the need for specific exercise [17]. The clinical questions were: *In*

adults with ankylosing spondylitis, which measures are beneficial for baseline mobility assessment in order to inform exercise prescription? What are the minimum requirements for monitoring these measures?

Results

No evidence was found comparing the effectiveness of an exercise program informed by individual assessment, to a standardised program - hence the rating of this recommendation as clinically based. However, a number of (largely non-controlled) cross-sectional studies found relationships between axial mobility (anthropometric) measures and self-reported domains such as physical function, disability and quality of life [18-21], Van Weely [22] found that self-reported function was typically reported as being more impaired than objectively measured function. Self-reported scores therefore do not substitute for objective measures, and hence the rationale for an accurate assessment that includes both subjective and objective components. The choice of AS-specific tools is further discussed at B1.1 and C2.1, but as a minimum, validated axial mobility measures and chest expansion should be completed. As reflected in the statement below, a combination of self-reported and objective information usefully informs exercise prescription and identifies where more detailed assessment may be indicated. Analysis of such tests is beyond the scope of this review, but many are simple and quick to perform in the clinical setting, and may be required to assess the consequences of more advanced AS on strength, balance or cardio-pulmonary function.

Recommendation 1: Assessment
Individual exercise prescription should be informed by a thorough and reproducible assessment which includes musculoskeletal and psychosocial factors, and AS-specific measures - including objective axial mobility and chest expansion. (CBR)

No direct evidence was found to answer the question regarding monitoring. However, in the experience of the WG, there is also rationale for longitudinal monitoring of AS anthropomorphical measures, in order to evaluate exercise effectiveness, assess change in mobility and provide personal feedback, which may be motivational. In clinical practice, patients appear to value the objective information provided by assessment and it appears to have a positive effect on exercise behaviour [23], hence the following recommendation.

Recommendation 2: Monitoring
Sufficient monitoring and feedback should be provided on an individual basis, to achieve confidence and competence with exercise, and to inform changing needs for exercise prescription. This is recommended at least annually, and more often as symptoms, function and mobility indicate. (CBR)

Safety

Background

The WG was anecdotally aware of single case adverse events associated with exercise, including spinal fracture/ cord injury, hip arthroplasty dislocation and spinal pseudarthrosis/ discitis. The clinical question was: *In adults with AS, what safety aspects should be considered in relation to exercise prescription?*

Results

Direct evidence for exercise safety issues (including adverse events) relating to AS was not found, therefore indirect evidence of secondary disease consequences was reviewed. The AS population includes people for whom the risks of exercise are higher than a non-AS population, secondary to:

(a) Small increases in cardio-vascular risk factors and ischaemic heart disease; [24].
(b) Decreased pulmonary function (in association with decreased axial mobility); [13, 25]
(c) Spinal osteoporosis, which appears related to disease activity and duration, and has an incidence of 18-67%; [26]
(d) Spinal fracture risk in established AS of between 14 and 19% [27], which (due to the biomechanics of an ankylosed spine) is more likely to result in spinal cord injury (SCI) than in a non-ankylosed spine [28], and,
(e) Impaired balance and righting reactions, again in association with spinal ankylosis [12]

Other less frequent but recognised complications of AS that may be impacted by inappropriate exercise include: discitis/ pseudarthrosis (most prevalent at T11/12 level) [29]; anterior total hip arthroplasty dislocation [30] and atlanto-axial subluxation [31].

Co-morbidity prevalence was consistently shown to be related to disease severity and/ or duration, so it should be emphasised that the additional risks described are largely restricted to those with more advanced disease. However, the potential consequence for an individual of an adverse event is high, and little attention has been paid to this aspect of exercise prescription to date. It seems likely that the benefits of exercise still outweigh the risks for almost all individuals, however, *appropriate* exercise prescription is paramount for those with more severe disease.

Recommendation 3: Safety
Throughout all aspects of exercise prescription, especially for those with more severe or advanced disease, the pathological changes of AS must be considered. These include the amount of bony change/ ankylosis, balance and mobility changes, osteoporosis, and cardiorespiratory consequences of the disease. (CBR)

Disease Management

Background

It is not known whether the beneficial effects of exercise in AS occur at a systemic (e.g. anti-inflammatory) or local (e.g. enthesis) level. In healthy adults, and those with a number of chronic diseases, exercise can produce systemic anti-inflammatory effects, [32-35], but interactions between exercise and pathology are complex. It may be that exercise can have either pro or anti-inflammatory consequences for individuals with inflammatory arthritis, depending on the type of exercise and the condition concerned [36]. Two clinical questions were generated by the WG on this topic: (1*) Is exercise effective in disease modification (reduction in progression), compared with no exercise?* and, (2) are exercises in combination with an anti-TNF*α medication more beneficial than medication alone?* [15].

Results

Insufficient evidence was found to determine whether exercise produces local and/ or systemic effects in AS, and so a recommendation regarding disease modification was not made. However, two RCTs [37, 38], two non-randomised experimental trials [39, 40] and one interrupted time series without controls [41] were identified in patients on anti-TNFα therapy. The trials consistently demonstrated the beneficial effect of a combination of anti-

TNFα therapy and an AS-specific exercise program, compared with either anti-TNFα treatment or exercise alone, for both self-reported measures (such as function and disease activity) and objective measures, such as the Bath Ankylosing Spondylitis Metrology Index (BASMI) [42]. Further detail is shown in Appendix B, section 3.

Recommendation 4: Disease Management
Individuals receiving anti-TNFα therapy should continue with regular exercise prescription as it confers an additional benefit to anti-TNFα therapy alone. (EBR, grade B)

AS-Specific Exercise

Background

Traditional goals of exercise in AS have focused on improving and/or maintaining physical function and posture by: mobility exercises for axial and peripheral joints; muscle strengthening (especially 'antigravity' muscles); stretching of specific muscle groups; and cardio-respiratory fitness [43]. The combination of soft tissue stretch and dynamic joint mobility exercises for 'tight' or shortened soft tissues/ restricted joints, and improved recruitment and strengthening of 'lengthened' muscles is thought to target the biomechanical, mobility and postural changes of AS. The clinical question was: *In adults with AS, is therapeutic (specifically prescribed) exercise aimed at:*

(a) improving mobility/ posture;
(b) increasing strength;
(c) improving cardiorespiratory fitness, and,
(d) improving function (balance, co-ordination, gait, agility and proprioception),

more beneficial for pain, mobility, disease activity and physical function than no exercise/ general advice only?

Results

There were eight systematic reviews (SRs) concerning exercise interventions that were widely available or could be reproduced in a non-residential setting. Three [6, 8, 9] included meta-analysis of outcome measures, with a consistent trend for small to medium effects (including pain, physical function, axial mobility, and other self-reported outcome

measures), in favour of various exercise interventions.

Eleven individual RCTs met our criteria, and most (nine out of eleven) met the commonly used benchmark for a 'good quality' study, with a score of six or more on the Physiotherapy Evidence Database (PEDro scale) [44]. The results are summarised in Tables 1 and 2, and in more detail in Appendix B (section B1.4 and table B1), and again show a high level of consistency for small to moderate benefits for pain, disease activity, axial mobility and function. This was confirmed by our meta-analyses of these studies, displayed as Forest plots at figure 2. Statistical heterogeneity was low for most outcomes (cervical mobility, finger to floor distance, chest expansion, pain and disease activity) but was moderate for lumbar flexion and substantial for physical function. Potential sources of heterogeneity in exercise trials include: the trial participants (in this case, disease severity is particularly relevant); exercise dosage (including variation in trial duration and exercise frequency, intensity and time); program design (for example, type of exercises, their delivery method and setting) and trial methodology and quality [45].

While these effects are small to modest, recent academic discussion has also highlighted the issue of therapeutic validity of trials [46], that is, whether the exercises described meet guidelines for dosages known to produce physiological improvements. In general, there was poor reporting of exercise goals, program design, outcome measures and adherence, and the links between these components were not specified. Dosage (particularly intensity) appeared to be insufficient in most trials [9].These factors may account for the trial effect sizes being somewhat smaller than those reported anecdotally by patients and clinicians.

Overall, the WG found that the consistent evidence of benefits for exercise in AS was sufficient to form recommendations focusing on axial mobility exercises plus stretch, strength, cardiopulmonary and functional fitness. Evidence for further specificity was not available, and the WG's clinical question regarding the best exercise program could not be fully answered, although benefits for specific types of exercise could also not be excluded. Given the large spectrum of disease activity, severity and variation in presentation of mobility impairment in AS, it seems likely that 'best practice' will continue to be an individualized program where exercises are selected to target an improvement (or prevention of deterioration) of identified postural, biomechanical and functional changes. Clearly there is overlap and interaction between the different exercise categories, but in a

balanced program each aspect should facilitate performance of the other, as shown visually in Figure 1.

Recommendation 5: AS-specific Exercise (Mobility)
Individual exercise prescription with an emphasis on spinal mobility is paramount for best management of AS. Maintaining mobility of peripheral joints is also essential. This can be achieved through a number of approaches. At this time we are unable to recommend one approach over another, therefore individual goals should be informed by assessment findings. (EBR grade A)

Recommendation 6: AS-specific Exercise (Other)
Stretching, strengthening, cardiorespiratory and functional fitness are important components to include in a balanced exercise program. (EBR grade B)

Physical Activity

Background

There is a large and compelling body of population-based evidence regarding the importance of physical activity (PA) for health, [47] resulting in national PA guidelines for 'healthy adults' in most countries. Most current guidelines are based on 150-300 minutes of moderate intensity, or 75-150 minutes of vigorous intensity PA per week, plus muscle strengthening at least twice per week [48, 49]. The WG was interested in the interpretation of such guidelines for people who have AS, the clinical question being: *which types of physical activity are beneficial for pain, mobility, disease activity and function?*

Results

There is long-standing consensus that sports/ activities involving high impact, such as some football codes, martial arts or distance road running should be avoided in AS due to the risk of symptom exacerbation or structural damage to an inflamed or ankylosed spine [43, 50]. Similarly, activities which excessively challenge balance may increase falls risk and should therefore be avoided. A recent hypothesis [51] suggests that mechanical stress may have a role in the disease pathology, and if proven this could further influence activity choices. For now, the pragmatic advice remains to avoid high impact activities, particularly in disease that is more active, severe or long-standing.

Regarding types of widely available leisure activities, three small RCTs investigated the effects of tai chi [52], swimming [53] and Pilates [54]. These activities combine aspects of mobility, strength and functional (neuromotor) training, suggesting that they could be beneficial in AS, and the trials demonstrated small to moderate improvements for self-reported and performance based measures. A larger survey of 1538 people with AS found an association with physical activity levels (PALs) and mobility, but evidence was not found for the superiority of one activity over another [55].

In summary, there was insufficient evidence to show that one type of activity is more beneficial – but there is no reason to suggest that people with AS would not benefit from maintaining PALs as per the general population. It seems likely that individuals with early AS would benefit from a different set (and greater range) of activities than those with later/ more advanced disease. In the latter case, safety factors are paramount and physical activity guidelines for an older population (such as the National Physical Activity Recommendations for Older Australians) [56] may be appropriate.

Recommendation 7: Physical Activity
Regular physical activity should be encouraged to promote general health, well-being and functional outcomes. (EBR, grade B)

Dosage

Background

FITT-VP [17] is a widely used framework for exercise dosage and comprises six components: Frequency (how often); Intensity (how hard); Time (duration) and Type, resulting in a total exercise Volume with the last component being 'Progression'. Exercise dosage should be considered for these parameters in all three of the exercise components shown in Figure 1, however, the many variables contributing to an individual's dose response (including genetics, pathology, physiology, psychosocial factors and settings/ environments [57]), mean that personalised adaptation of any recommendations is desirable. A further consideration is the concept of intensive (larger volume) exercise doses that may be indicated in the short-term for a specific purpose, as opposed to sustainable (less intensive, smaller volume) doses for the long-term. For mobility, posture and stretch exercise, there is obviously an optimal level that can be achieved: once this is attained and is stable, a 'maintenance' dose (rather than progression) is appropriate. The

clinical question was: *In adults with AS, what dosage of exercise is beneficial for pain, mobility, disease activity and function?*

Results

The most extensively analysed exercise dosage is that for PALs in healthy adults, as per national physical activity guidelines [48, 49]. These are aimed at chronic disease *prevention*, and the evidence for long-term *therapeutic* exercise is less clear.

As can be seen from Table 3, there were limitations to the reported dosage information in included RCTs. In general, information on exercise frequency was available, with 'daily' frequency reported in five out of 11 studies [52, 54, 58-60], but with a range down to once per week in one study [61]. Other components of exercise volume were often not reported, including exercise progression.

The association between volume of *habitual* exercise in individuals with AS, and measures of pain, disease activity, mobility and function were examined in 13 cross-sectional studies, and these are presented in table 4. Again, it was difficult to differentiate between exercise types and reported dosage parameters, and all relied on self-reported measures except Arends [62] who measured PALs with an accelerometer. Following a survey of 4282 people, Santos [63] suggested that exercise consistency is the most important factor. This term was not specified but appeared to relate to 2 to 4 hours of exercise per week on a sustained basis. This was supported by Ward [64] in the USA, who found that back exercises on more than five days per week, and recreational exercises for more than 200 minutes per week, were associated with a decrease in pain and stiffness and improvement in function. The higher frequency of back exercises was also associated with slower progress of functional disability over five years. There was no direct evidence to suggest a minimally effective stretch time.

Exercise dosage to address the strength, cardiorespiratory and functional (balance/ motor skills) consequences of AS received little attention in the literature. Dagfinrud's [9] study found no trials that met ACSM criteria for physiological effectiveness for strengthening exercises, and only one trial (out of 12) met the criteria for cardio-respiratory exercise. However, it should also be noted that there is a curvilinear dose-response relationship with a steep initial slope [65] and most benefit is therefore to be gained by individuals moving

from a sedentary lifestyle to performing some regular exercise, in other words, 'some regular exercise is better than none'. This may be pertinent to the significant proportion of people with AS who experience persistent pain and/ or fatigue [66], particularly when considering a commencement exercise dosage.

In summary, the relative influence of many variables is unique for each person, so a precise 'one size fits all' dosage is not possible, and this is reflected in the recommendation. Care should be taken to balance an individual's exercise capacity with attaining an adequate dose for effectiveness. Short-term, more intensive exercise dosage may be indicated to achieve a specific goal. However, long-term 'maintenance' AS-specific dosages should be realistic and aim for high frequency (five or more days per week) and sustainability. This may require compromise from the 'ideal' but the dose-response curve suggests that this may be a better outcome than short-lived attempts at unsustainable doses.

Recommendation 8: Dosage
Exercise frequency, intensity, duration and type must be tailored to the person's assessment findings, goals and lifestyle.
(a) For mobility, stretch and postural exercise, consistency is the most important factor
(b) For other exercise types, national physical activity guidelines may require modification. Consideration should be given to disease stage, activity and progression, whilst aiming for optimal effectiveness. (EBR, grade C)

Adherence

Background

The World Health Organisation in its 2003 report 'Adherence to long-term therapies: evidence for action' defined adherence as 'the extent to which a person's behaviour….corresponds with agreed recommendations from a health care provider', and further pointed out that an increase in adherence may be much more effective than a specific improvement in treatment for a population [67]. For people with AS, the data available (table 4) suggests that this is applicable. Predictors for low levels of exercise in cross-sectional studies appear inconsistent, as they include: less disability [19]; increased pain [68, 69], increased body mass index (BMI) [70] and lower spinal mobility [62]. The

relevant clinical question was therefore: *which interventions are beneficial for supporting adherence to an exercise plan?*

Results

Adherence was investigated by Barlow [71] in the 1990's, who noted positive short-term effects on adherence with self-help groups and education, but long-term effects were not found. Only one lower quality RCT of participants with AS was found for which exercise adherence was a primary aim [72], and long-term information was not provided.

Due to the paucity of research specific to AS, systematic reviews investigating strategies to increase adherence to exercise for chronic musculoskeletal conditions were also considered. A Cochrane review [73] looking at musculoskeletal pain in adults found moderate evidence that exercise adherence can be enhanced, but identified an urgent need for good quality research into long-term adherence to exercise interventions. Until that time, the authors recommended that patient preference should direct exercise type and setting: however, it should be noted that AS was a specific exclusion from this review. Conn in 2008 investigated physical activity interventions in adults with arthritis [74], and also the effects of education to increase PALs in adults with chronic illness [75]. Again, there was evidence that PALs can be positively influenced by interventions, with an effect size for educational strategies of 0.45, equivalent to 48 minutes of physical activity per week. The former study was a large evidence synthesis (22,257 subjects with chronic conditions) and suggested the largest educational effects were those targeting physical activity behaviour, reinforced by some sort of PAL monitoring. The latter study found a number of strategies that promote PALs: these are summarised in table 5 and reflected in the adherence recommendation.

Recommendation 9: Adherence
It is important to assess adherence with regular exercise, encourage motivation and promote ongoing self-management (EBR, grade B)

Exercise Setting

Background

A number of settings for exercise in AS have been studied, including: home; clinic/ out-

patient; gymnasium, out-patient hydrotherapy pool; other leisure activity/ sporting environments, spa resort/ balneotherapy centres (often residential); and in-patient hospital settings. Balneotherapy refers to baths of warm, mineralised water, usually in combination with both active exercises and more passive treatments such as massage or mud packs [76]. Many countries lack access to traditional spa/ balneotherapy centres and so this is not a widely available exercise option, however, 'aquatic physiotherapy' and 'warm water exercise' are moderately available. Residential or hospital in-patient treatment is much less widely available than in the past. Also relevant here is the mode of delivery, that is, whether the exercise was performed as part of a group and with or without health professional 'supervision'. The clinical question was therefore: *in adults with AS, which widely available exercise settings and modes of delivery are beneficial for pain, disease activity, mobility and function?*

Results

The Cochrane review of physiotherapy (exercise based) interventions for ankylosing spondylitis included 11 trials, with a total of 763 participants, published prior to January 2007 [8]. The outcomes analysed were: pain, stiffness, spinal mobility, physical function and patient global assessment, and all interventions were more beneficial than no intervention or 'usual care'. In-patient spa exercise therapy (an exclusion from our study) plus group therapy was found to be more effective than group therapy alone; individual home-based or supervised exercise programs were better than no intervention, but supervised group physiotherapy was better than home exercises.

Four further RCTs have been published (Appendix B, section 1.8) but these collectively demonstrate the difficulties in determining the effects of exercise type versus setting versus mode of delivery [37, 53, 54, 77]. Although different exercise settings appear to play a role in overall outcome, it is not possible to quantify whether benefits are due to the change in setting or environment, or the consequential support for motivation, adherence and higher exercise dosage that may arise from supervision and/ or a group mode of delivery. Clinical experience suggests that warm water exercise may be particularly beneficial for more long-standing or severe disease. Unfortunately, since it is not possible to separate the effects of exercise in warm water from other passive components of spa therapy, there is currently insufficient evidence to support this clinical impression. Hence, the WG consensus was

that personal preference, local availability and dosage are more important aspects than setting. However, if available, group and / or warm water exercise are likely to provide additional benefit.

Recommendation 10: Settings
Priority should be given to patient preference in exercise choice to enhance adherence and optimise positive outcomes (CBR)

3.5 Discussion

This consensus statement provides the first set of comprehensive exercise recommendations to guide practitioners' exercise prescription in AS with practical information. As a result of the consensus process, we developed a framework (Figure1) for considering all clinically relevant aspects of exercise prescription for people with AS, which has the potential to be adapted to other chronic musculoskeletal conditions, such as osteoporosis or osteoarthritis.

The process we followed had a number of strengths and limitations. The WG brought considerable experience and expertise in the clinical application of exercise in AS, and the development of key topic areas facilitated the investigation of all the important facets of exercise prescription in a way that has not been previously attempted. However, there were also some limitations to the study. For pragmatic reasons only English language papers were considered, and papers were initially selected by one author only: however, included papers were subsequently independently reviewed by a second author for suitability. Studies of those with axial spondyloarthritis were not included, and more focus on this group may be desirable in future. Although one member of the WG has AS, and additional patient input was obtained once the draft recommendations were developed, this process could have been strengthened by inclusion of people with AS earlier in the process. Professions other than physiotherapy are also involved in exercise prescription, and broadening of the representation on the WG could be considered in future reviews. Although the HP survey results were comparable to external validity testing for other rheumatology recommendations [78], a broader range of participants may have strengthened the feedback process. Lastly, in clinical practice, exercise may be combined with other non-pharmacological modalities, such as joint mobilisation [79], and

investigation of such treatment combinations was beyond the scope of this review.

Combining systematic reviews with consensus recommendations is a lengthy process. In order to address the time lag between the initial searches and publication, the review for AS-specific exercise was repeated for publications until 1st July 2015. A total of five SRs (two with meta-analysis) and seven RCTs met the inclusion criteria. The SRs added weight to the recommendations in terms of support for exercise for improved outcomes [80-84]. More specifically, there was support for: 'multi-modal' programs (the main exercise types as shown in Figure 1) [80, 85-87]; cardio-vascular training (as per recommendation 6) [88] and the synergistic effect of exercise and anti-TNFα medication (recommendation 4) [80, 82]. There was preliminary evidence for: 'McKenzie' (a protocol of repeated spinal mobility exercises) in early AS [89]; inspiratory muscle training [90, 91], and aquatic exercise [92] in cohorts with more established disease. However, there was agreement that 'the most effective exercise protocol remains unclear [86]. We believe that additional studies targeting sub-groups such as early or later AS (and the spondyloarthropathies) would enable greater specificity regarding exercise recommendations in the future, however, the basic framework (Figure 1) will apply to all. With regard to exercise settings and supervision, a SR of home-based exercise found small to moderate benefits for pain, function, disease activity and depression [81]. However, reviews by Gianotti and O'Dwyer [80, 84] and a 12-month follow-up to an RCT [93] support supervision and group components, and a large multi-centre trial in Portugal found only small measureable gains for a program with minimal supervised exercise practice [94]. These findings have been reflected as an additional PP (recommendation 10).

As previous authors have noted [9], major concerns regarding trial quality and clinical relevance remain. In general, future trials should better describe the exercise interventions and dosage, and use validated objective measures, such as the BASMI 10 point scale [95]. Despite consistent findings that exercise is effective in AS, the potential interactions between the physiological effects of exercise and the pathological processes have yet to be clarified. More knowledge about this could facilitate precise targeting of exercise effects by more informed program design. Investigation of different patient groups (such as those with early, well-controlled AS versus long-standing, advanced disease) could determine if stratification of patient groups would increase effectiveness – it seems unlikely that 'one size' will ever 'fit all'. Further evaluation of the effect of specific programs to address

strength, cardiorespiratory and functional factors (such as balance), is also warranted. Exercise program design should also be clearly linked to treatment aims and address physiological effectiveness, including progression: given that some subjects may start from a relatively low baseline, longer studies are therefore required. Such programs would allow better titration of dosage and thus may reflect the larger effect sizes that people with AS and clinicians often report. Accurate physical activity trackers should in future provide better objective data on exercise dosage, and studies that consider long-term outcomes and self-management strategies would be more relevant to the reality of limited availability of resources. Lastly, this would better inform the most urgently needed area of research, which is identified in this review as long-term adherence to exercise strategies.

3.6 Conclusion

The evidence found was of mixed quality, but consistently supported the beneficial effects of exercise in AS. However, lower quality research in some areas means that the current approach remains personalised and targeted to individual therapeutic goals. The ten recommendations are specific enough to be clinically useful, but flexible for adaptation to the needs of all individuals. This new framework is summarised in figure 1, and has the potential to be adapted for other chronic musculoskeletal conditions. Although developed for the Australian context, the recommendations would also apply to other regions, particularly where spa or residential centres are not routinely available, or to anyone seeking information on long-term exercise strategies. Widespread dissemination and implementation of the guidelines will be important to ensure a more consistent approach to AS exercise management, and optimise outcomes for people with this condition.

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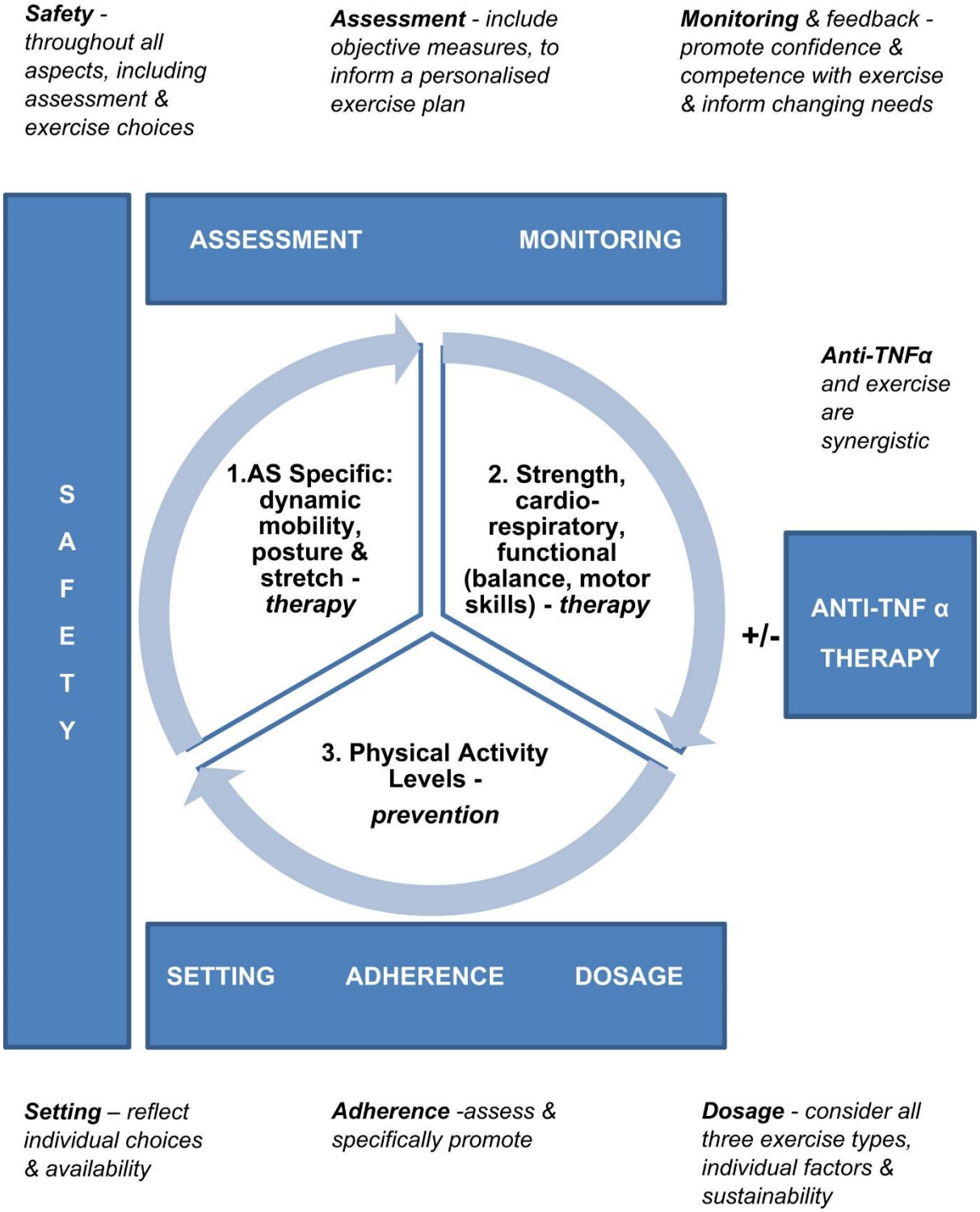
3.9 Figures and Tables

Figure 3.1 Framework for Exercise and Ankylosing Spondylitis

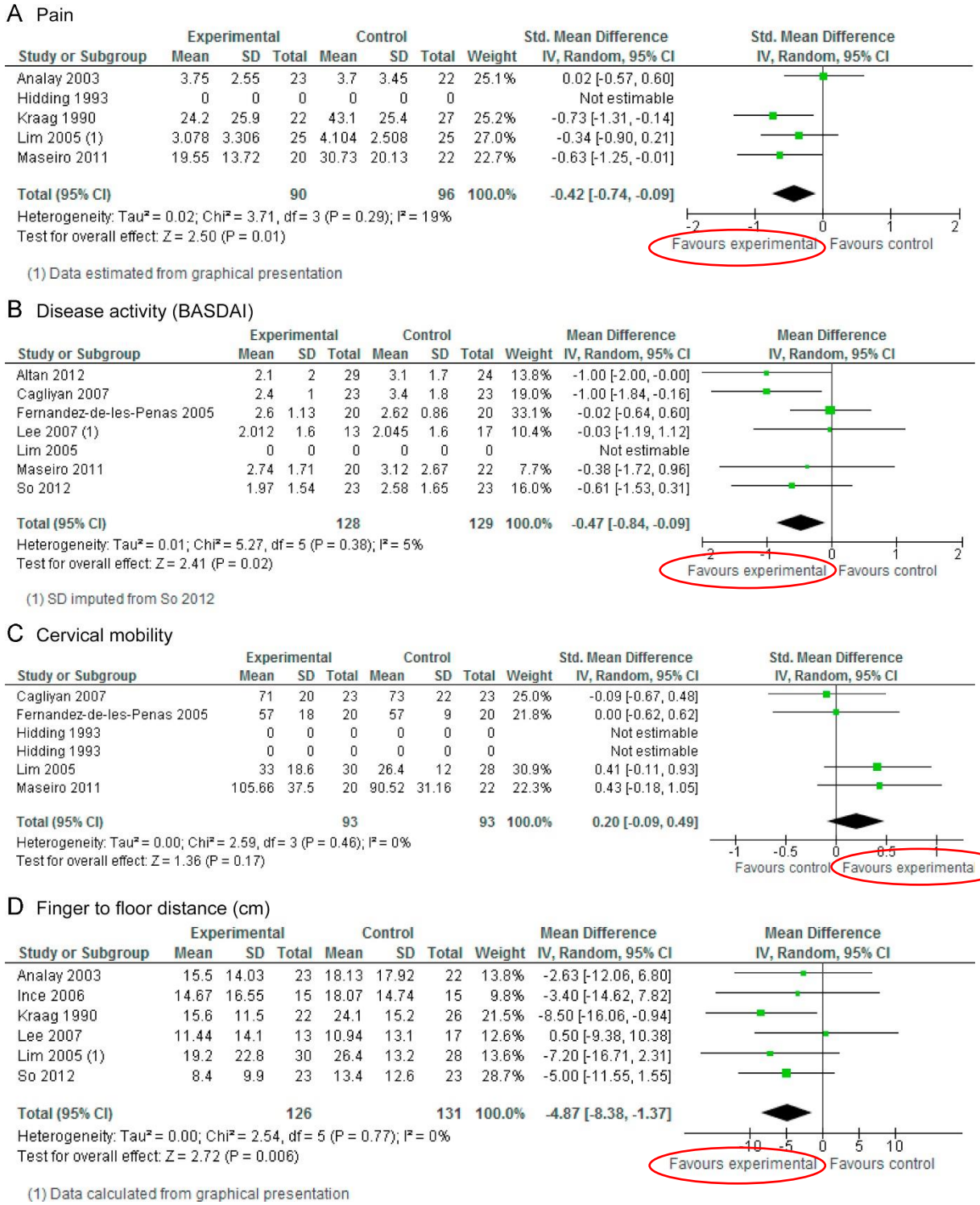


Aims:

1. Address primary (musculo-skeletal) consequences of AS
2. Address secondary consequences of AS (cardio-resp, balance, osteoporosis)
3. Facilitate physical activity according to national guidelines, with modification for AS symptoms, severity, activity & duration as required

The three main types of exercise for a balanced program are shown in the circle, numbered for the sequence in which they would usually be addressed. The upper segments of the circle indicate exercise types that are therapeutic, that is, address specific aspects of AS management. The lower segment addresses exercise for maintenance of health, similar to the general population. The arrows indicate that there is interaction between the exercise types. The surrounding bars show key aspects of exercise prescription for consideration throughout the process, from initial assessment to ongoing practice. Finally, the recommendations are broadly applicable and continue to be relevant, even after commencement of anti-TNFα therapy.

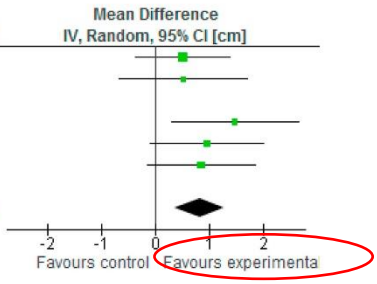
Figure 3.2 Forest plots of meta-analyses



E Chest expansion (cm)

Study or Subgroup	Experimental Mean [cm]	SD [cm]	Total	Control Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Altan 2012	4.5	2	29	4	1.2	24	28.3%	0.50 [-0.37, 1.37]
Analay 2003	4.73	1.94	23	4.22	2.13	22	15.1%	0.51 [-0.68, 1.70]
Hidding 1993	0	0	0	0	0	0		Not estimable
Ince 2006	3.23	1.6	15	1.77	1.67	15	15.7%	1.46 [0.29, 2.63]
Maseiro 2011	4.52	1.63	20	3.57	1.85	22	19.4%	0.95 [-0.10, 2.00]
So 2012	4.17	1.84	23	3.33	1.61	23	21.5%	0.84 [-0.16, 1.84]
Total (95% CI)			**110**			**106**	**100.0%**	**0.81 [0.35, 1.28]**

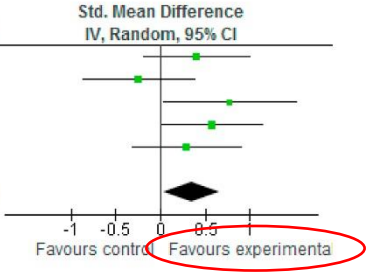
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)



F Lumbar flexion

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Analay 2003	5.26	3.16	23	3.96	3.16	22	21.5%	0.40 [-0.19, 1.00]
Fernandez-de-les-Penas 2005	2.4	1.1	20	2.7	1.3	20	19.9%	-0.24 [-0.87, 0.38]
Ince 2006	13.83	1.62	15	12.48	1.77	15	15.0%	0.77 [0.03, 1.52]
Kraag 1990	11.6	1.6	24	10.7	1.5	27	23.1%	0.57 [0.01, 1.13]
Maseiro 2011	94.11	23.74	20	86.63	26.13	22	20.5%	0.29 [-0.32, 0.90]
Total (95% CI)			**102**			**106**	**100.0%**	**0.35 [0.02, 0.67]**

Heterogeneity: Tau² = 0.04; Chi² = 5.41, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 2.11 (P = 0.04)

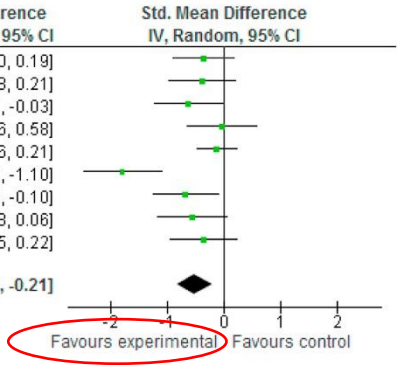


G Physical Function

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Altan 2012	1.7	1.6	29	2.3	1.7	24	11.5%	-0.36 [-0.90, 0.19]
Analay 2003	20	16.76	23	27.31	20.42	22	10.8%	-0.39 [-0.98, 0.21]
Cagliyan 2007	1.6	1.4	23	2.8	2.3	23	10.7%	-0.62 [-1.21, -0.03]
Fernandez-de-les-Penas 2005	45.7	20.6	20	46.5	21	20	10.3%	-0.04 [-0.66, 0.58]
Hidding 1993 (1)	-1.6	3.98	67	-1.1	3.98	68	15.0%	-0.12 [-0.46, 0.21]
Kraag 1990	-4.14	2.92	22	-0.08	1.39	25	9.4%	-1.78 [-2.47, -1.10]
Lim 2005 (2)	1.6	2.47	25	3.42	2.85	25	11.1%	-0.67 [-1.24, -0.10]
Maseiro 2011	2.17	1.24	20	3.13	2.01	22	10.4%	-0.56 [-1.18, 0.06]
So 2012	0.75	1.17	23	1.26	1.56	23	10.9%	-0.36 [-0.95, 0.22]
Total (95% CI)			**252**			**252**	**100.0%**	**-0.51 [-0.81, -0.21]**

Heterogeneity: Tau² = 0.13; Chi² = 21.02, df = 8 (P = 0.007); I² = 62%
Test for overall effect: Z = 3.34 (P = 0.0008)

(1) Pre-post test change score used as outcome SD not available
(2) Data estimated from graphical presentation



(A) Pain; (B) disease activity (BASDAI); (C) cervical mobility; (D) finger to floor distance (cm); (E) chest expansion; SD = standard deviation; CI = confidence interval.

Meta-analyses of exercise trials for outcome measures of pain, disease activity, mobility (cervical mobility, finger to floor distance, chest expansion and lumbar flexion) and physical function, summarised as Forest plots for included studies. A random effects model was used due to the heterogeneity of the interventions. The boxes represent point estimates for each study, their size being proportional to the size of study. The horizontal bars represent 95% confidence intervals and the diamond the pooled effect size. Mean differences were calculated where the same scale was used for all studies, and standardised mean differences (SMD) calculated where different scales were reported.

Box 3.1 Recommendations and Practice Points

Recommendation 1: Assessment

- **Individual exercise prescription should be informed by a thorough and reproducible assessment which includes musculoskeletal and psychosocial factors, and AS-specific measures - including objective axial mobility and chest expansion. (CBR)**

- The Bath Ankylosing Spondylitis Metrology Index (BASMI) [1] is the most widely reported, validated objective axial mobility measure
- BASMI is associated with quality of life, physical function and psychological status
- The BASMI 10-point scoring scale is recommended over the 3-point scale
- Imaging review/ discussion with medical team may be indicated for more advanced disease
- Tape-based hip internal rotation is a responsive measure for hip involvement
- Strength, balance or cardiorespiratory function should be assessed as required

Recommendation 2: Monitoring

Sufficient monitoring and feedback should be provided on an individual basis, to achieve confidence and competence with exercise, and to inform changing needs for exercise prescription. This is recommended at least annually, and more often as symptoms, function and mobility indicate (CBR)

- Feedback, particularly mobility measures, can be important for exercise adherence.
- BASMI raw scores are more sensitive to change than index scores
- In BASMI, lumbar side flexion is the most sensitive to change
- The Edmonton AS Metrology Index (EDASMI) [2] may be useful for patient self-monitoring

Recommendation 3 : Safety

Throughout all aspects of exercise prescription, especially for those with more severe or advanced disease, the pathological changes of AS must be considered. These include the amount of bony change/ankylosis, balance and mobility changes, osteoporosis, and cardiorespiratory consequences of the disease (CBR)

Most types of exercise are safe for the majority of patients. However, the following require assessment on a case by case basis, and may be contra-indicated in more advanced AS:

- High impact exercise/ physical activity (e.g. contact sports, martial arts, four wheel driving, boating in rough seas, fairground rides)
- balance, postural stability or cardiorespiratory function (in a non-controlled environment)
- High velocity or strongly resisted exercise, especially trunk flexion/ rotation
- Excessive spinal or peripheral joint mobility gain where there is adjacent ankylosis

- Exercise which excessively challenges
- Excessive end range mobility gain following total hip replacement

Recommendation 4: Disease Management

Individuals receiving anti-TNFα therapy should continue with regular exercise prescription as it confers an additional benefit to anti-TNFα therapy alone (EBR, grade B)

- Exercise could theoretically be a mediator of inflammation in AS, but trial results have been conflicting
- Stabilisation with anti-TNFα therapy can be a 'window of opportunity' to optimise mobility and physical fitness

Recommendation 5: AS-Specific Exercise – Mobility

Individual exercise prescription with an emphasis on spinal mobility is paramount for best management of AS. Maintaining mobility of peripheral joints is also essential. This can be achieved through a number of approaches. At this time we are unable to recommend one approach over another, therefore individual goals should be informed by assessment findings. (EBR grade A)

- Mobility goals may vary from restoration of full spinal range and normal posture [early, well controlled disease], to maintenance of existing range [later disease].
- Exercise choice (e.g. specific proprioceptive neuromuscular facilitation techniques) can be tailored to target movement or functional deficits

Recommendation 6: AS-Specific Exercise -Other

Stretching, strengthening, cardiopulmonary and functional fitness are important components to include in a balanced exercise program (EBR grade A)

- There is preliminary evidence for (modified) Pilates and tai chi, incentive spirometry and global postural re-education as effective modalities

Recommendation 7: Physical Activity

Regular physical activity should be encouraged to promote general health, well-being and functional outcomes (EBR, grade B)

- No one activity has been found to be superior
- Regular interruption of sedentary activities should also be encouraged
- Occupational, transport and leisure activities contribute to total physical activity levels

Recommendation 8: Dosage

Exercise frequency, intensity, duration and type must be tailored to the person's assessment findings, goals and lifestyle.

(a) For mobility, stretch and postural exercise, consistency is the most important factor

(b) For other exercise types, national physical activity guidelines may require modification. Consideration should be given to disease stage, activity and progression, whilst aiming for optimal effectiveness (EBR, grade C)

- Factors which may indicate modification of baseline exercise dose include: pain/ fatigue; disease activity and any secondary AS consequences (cardio-respiratory, ankylosis, osteoporosis, balance impairment)
- Dosage progression (titration) should balance individual exercise response with training for physiological change
- Mobility exercise can be incorporated in regular breaks from sitting
- Short-term more intensive doses may be appropriate for specific purposes.

Recommendation 9: Adherence

It is important to assess adherence with regular exercise, encourage motivation and promote ongoing self-management (EBR, grade B)

- Group settings and monitoring have been shown to support adherence in AS

Recommendation 10: Exercise Setting

Priority should be given to patient preference in exercise choice, to enhance adherence and optimise positive outcomes (CBR)

- AS-specific group therapy and warm water exercise may be beneficial adjuncts

to an individual's regular home exercise program.

Recommendations are shown in bold type, with supporting practice points where there was a need to provide practical guidance to support the recommendation. Development details, definitions and evidence are shown in Appendix B (recommendations) and Appendix C (practice points).

EBR Evidence Based Recommendation, based on body of evidence[3]:

grade A - Body of evidence can be trusted to guide clinical practice

grade B - Body of evidence can be trusted to guide clinical practice in most situations

grade C – Body of evidence provides some support for recommendation, but care should be taken in its application

grade D – Body of evidence is weak and recommendation should be applied with caution

CBR Consensus Based Recommendation, developed by the WG where there was insufficient direct (or poor quality) evidence to answer the clinical question

1. Jenkinson T, Mallorie P, Whitelock H, Kennedy G, Garret S, Calin A: **Defining Spinal Mobility in Ankylosing Spondylitis (AS). the Bath Metrology Index**. *The Journal of Rheumatology* 1994, **21**(9):1694-1698.
2. Maksymowych WP, Mallon C, Richardson R, Conner-Spady B, Jauregui E, Chung C, Zappala L, Pile K, Russell AS: **Development and validation of the Edmonton Ankylosing Spondylitis Metrology Index**. *Arthritis Rheum* 2006, **55**(4):575-582.
3. Australian Government National Health and Medical Research Council (NHMRC): **additional levels of evidence and grades for recommendations for developers of guidelines**. In., vol. 2009: NHMRC; 2009.

Table 3.1: AS-Specific Exercise: Interventions and outcomes (pain, disease activity and physical function)

Study	Treatment Groups	PEDro Score /10	No. in group	Duration	Assess. point(s)	Outcome SMD (95%CI)		
						Pain	Disease activity	Physical function
Altan 2012	I: Pilates with trainer, x3/week C: standard treatment program	8	30 25	12 weeks	Week 12 Week 24		-1.00 (-2.00, -0.00)	-0.36 (-.90,0.19)
Analay 2003	I: AS education session; supervised exercise programme, x3/week C: AS education session; instruction to perform the same exercises at home x3/week; weekly progress phone call	7	23 22	6 weeks	Week 6 Week 12	0.02 (-.57,0.60)		-0.39 (-.98,0.21)
Cagliyan 2007	I: AS education session; supervised exercise program x2/ week C: AS education session; instruction to perform exercises at home; telephone follow-up	4	23 23	12 weeks	Week 12 Week 24		-1.00 (-1.84, -0.16)	-0.62 (-1.21, -0.03)
Fernandez-de-las-Penas 2005	I: Weekly supervised exercise session, Global Postural Re-education method C: Weekly supervised exercise, using conventional exercises	6	20 20	16 weeks	Week 16		-0.02 (-0.64, 0.60)	-0.04 (-.66.0.58)
Hidding 1995	I: Weekly group physiotherapy: mobility/ strengthening exercises, sports & hydrotherapy, plus daily individual home exercise program C: Daily individual exercise program	7	67 68	36 weeks	Week 36	not estimable		-0.12 (-0.46, 0.21)
Ince 2006	I: Supervised multimodal exercise program (warm-up, aerobic step, stretching & pulmonary exercises) plus information on exercise benefits C: Information on exercise benefits only	7	15 15	12 weeks	Week 12			

Kraag 1990	I: Home physiotherapy: combination of education, passive techniques plus therapeutic exercise according to individual problem list C: No treatment	8	22 26	16 weeks	Week 16	-0.73 (-1.31, -0.14)		-1.78 (-2.47,-1.10)
Lee 2007	I: Tai chi for RA program; plus home practice; tai chi video; telephoned by researchers x2/week C: no structured exercise program; telephoned by researchers x2/ week	6	13 17	8 weeks	Week 8		-0.03 (-1.19, 1.12)	
Lim 2005	I: Home exercise program (for muscle relaxation, flexibility, strength, breathing and posture) taught individually; requested practise was daily x 30 minutes C: no intervention	6	25 25	8 weeks	Week 8	-0.34 [-0.90, 0.21]	Not estimable	-0.67 (-1.24, -0.10)
Maseiro 2011	I- A: Educational/ behavioural meetings x 2, then exercise training x 2/ week: flexibility, stretches, proprioceptive, breathing & endurance. Home practice x3-4 / week requested; exercise DVD and monthly phone calls. I- B: Educational / behavioural meetings only C: No intervention	7	20 20 22	6 weeks	Week 8 Week 24	-0.63 (-1.25, -0.01)	-0.38 (-1.72, 0.96)	-0.56 (-1.18, 0.06)
So 2012	I: Incentive spirometer exercise program daily, plus education/ conventional home exercise program (spinal flexibility, stretches and breathing exercises) C: Education and individual counselling plus instruction in a conventional home exercise program	6	23 23	16 weeks	Week 16		-0.61 (-1.53, 0.31)	-0.36 (-0.95, 0.22)
Overall Effect	**NB. All in favour of intervention groups**					**-0.42 (-0.74, -0.09)**	**-0.47 (-0.84, -0.09)**	**-0.51 (-0.81, -0.21)**

I Intervention group; C Contol group; MD Mean Difference; SMD Standardised Mean Difference; PEDro Physiotherapy Evidence Database; VAS Visual Analogue Scale; BASDAI Bath Ankylosing Spondylitis Disease Activity Scale; BASFI Bath Ankylosing Spondylitis Functional Index

Table 3.2 AS Specific Exercise: Axial mobility interventions and outcomes

Study	Exercise Type	Mobility/ stretch exercise type						Mobility outcomes			
		DF	AcS	BS	PS	PNF	U	Lumbar flexion SMD [95%CI]	Cervical mobility SMD [95%CI]	Chest expansion MD cm [95%CI]	Fingertip to floor distance MD cm [95%CI]
Altan 2012	Pilates	X					X			0.50 [-0.37, 1.37]	
Analay 2003	Multi-modal						X	0.40 [-0.19, 1.00]		0.51 [-0.68, 1.70]	-2.63 [-12.06, 6.80]
Cagliyan 2007	Multi-modal						X		-0.09 [-0.67, 0.48]		
Fernandez-de-las-Penas 2005	Global Postural Re-education	X			X	X		-0.24 [-0.87, 0.38]	0.00 [-0.62, 0.62]		
Hidding 1995	Mobility						X	Not estimable	Not estimable	Not estimable	
Ince 2006	Multi-modal		X		X			0.77 [0.03, 1.52]		1.46 [0.29, 2.63]	-3.40 [-14.62, 7.82]
Kraag 1990	Mobility					X		0.57 [0.01, 1.13]			-8.50 [-16.06, -0.94]
Lee 2007	Tai chi						X				0.50 [-9.38, 10.38]
Lim 2005 *	Not specified						X		0.41 [-0.11, 0.93]		-7.20 [-16.71, 2.31]
Maseiro 2011	Multi-modal	X			X	X		0.29 [-0.32, 0.90]	0.43 [-0.18, 1.05]	0.95 [-0.10, 2.00]	
So 2012	Inventive spirometer						X			0.84 [-0.16, 1.84]	-5.00 [-11.55, 1.55]

Overall Effect	**NB. All in favour of intervention groups**							**0.35 [0.02, 0.67]**	**0.20 [-0.09, 0.49]**	**0.81 [0.35, 1.28]**	**-4.87 [-8.38, -1.37]**

DF Dynamic Flexibility; PNFProprioceptive Neuromuscular Facilitation; BS Ballistic Stretch; U Unspecified ; PS Passive Static Stretch
* Data estimated from graphical presentation ; AcS Active Stretch; SMD Standardised Mean Difference; MD Mean Difference

NB. All effects in favour of intervention group

Table 3.3 RCT exercise volume in individuals with AS, compared with pain, disease activity, mobility or function

Author	Country	Frequency (intervention group)	Intensity	Time in minutes/ week (session length if reported)	Type	Statistically significant beneficial associations with pain, disease activity, mobility or function
Altan 2012	Turkey	Daily	n/a	210 balneotherapy; 210 HEP (30 min sessions)	HEP + balneotherapy vs HEP only	Pain, BASDAI, range of mobility measures, BASFI – for both groups
Analay 2003	Turkey	X3/week	'to individual tolerance'	150 (50 min sessions)	Stretch, mobility, strength, aerobic	Pain; BASFI
Cagliyan 2007	Turkey	X2/week	n/a	120 (60 min sessions)	Joint/ spinal mobility, stretching, strength, respiration, posture	Pain, BASDAI, mobility and BASFI
Fernandez-de-las-Penas 2005	Spain	X1/week	Mobility 2x 8-10 reps; Stretches up to 4 minutes	60	Global Postural Re-education	Mobility; function
Hidding 1995	Netherlands	X1/week (group) + daily HEP	n/a	180 (group); 156 (HEP)	Physical training (60); sports(60); hydrotherapy (60)	Thoraco-lumbar mobility
Ince 2006	Turkey	X3/week	Low intensity aerobic (metronome to standardise intensity)	150 (50 min sessions)	Stretch, aerobic, chest expansion	Range of mobility measures; physical work capacity; vital capacity
Kraag 1990	Canada	'Daily'	n/a	n/a	Individual exs program + manual techniques	Finger to floor distance & function
Lee 2007	South Korea	Instruction x2/ week; daily practice (x2 daily for last 2 weeks)	n/a	315 (45 min sessions)	Tai chi for RA (warm up, 21 tai chi movements, cool down)	BASDAI; finger to floor distance
Lim 2005	South Korea	'Daily'	n/a	210 (30 min sessions)	HEP – mobility; strength; posture	Pain; mobility; function

Masiero 2011	Italy	X2/week (group) X3-4/week (HEP)	Mobility 2x10 reps; Stretches 30-40 seconds; aerobic- low speed, no resistance	120 (60 min group session) HEP n/a	Mobility, breathing exs, balance, posture, proprioception, stretch, strength, aerobic (walk, treadmill, cycle)	BASDAI, BASFI, BASMI
So 2012	South. Korea	Daily	Incentive spirometer breath holds 3-5 seconds	Incentive spirometer 350; HEP 350	HEP- mobility; stretch; chest expansion	Mobility; BASDAI, BASFI (both groups); pulmonary function for incentive spirometer group

Table 3.4 Habitual ('unsupervised') exercise volume in individuals with AS, and associations with pain, disease activity, mobility or function

Author	Country	N	Frequency	Intensity	Time/ week	Type	Other findings
Arends (2011)	The Netherlands	55	n/a	n/a	Measured in Kilo counts / day (accelerometer) but values not stated	PAL for 7 days	PAL negatively associated with inflammatory markers, BASFI; positively associated with Schobers test, lateral flexion & neck rotation; no association with chest expansion, BASDAI or occiput to wall distance
Brodin (2007)	Sweden	50	Never 22%; ≤ x1/week 18%; 1-2x/week but irregular 2%; ≥ x2/ week 58%	n/a	n/a	Pool exs; walk; resistance exs; aerobic exs; cycle; floorball; golf; jogging; Nordic walk; tai chi	Higher exercise frequency (>2x/week) predicted by long duration of symptoms, prior exercise habits, higher disease activity and living alone
Carter (2006)	UK	131	Daily 35%;3–5 x/ week 26%; 1–2 x/week 27%; < 1x/ week or none 12%	n/a	n/a	Walk 73%; swim 27%; HEP 18%; pool exs 14%; cycle 11%	No associations found for pain, BASDAI
Cooksey (2012)	UK	326	Moderate-high PAL by IPAQ-SF score	n/a	n/a	n/a	PALS independently associated with function
Falkenbach (2003)	Austria	132	>x2/week 19%; 1-2x/week 36%; <x1/week 45%	n/a	n/a	Cycle 22%; swim 21%; walk 10%; other sports 47%	PALS positively associated with mobility
Falkenbach (1999)	Austria	132	<x1/week 36%; 1-3x/week 46%; >x3/week 18%	n/a	n/a	AS specific HEP	Exs frequency positively associated with HAQ score
Fitzpatrick (2006)	Ireland	198	AS-specific 5-7 days/week 20%	n/a	PAL>200 mins/week 30%	n/a	Barriers to exercise were lack of time and motivation , fear of symptom exacerbation and fatigue
Haglund (2012)	Sweden	2167	Criteria met for moderate (x5-7/ week) or vigorous (2-3/week) physical activity 68%	Criteria for mod. to vigorous PAL met / not met	Exercise sessions>30 mins/ week met or not met	n/a	68% met WHO PAL recommendations for healthy adults

O'Shea (2008)	UK	61	Walk 3x/week 35%; stretch 3x/week 32%	n/a	n/a	n/a	High scores for both perceived benefits and perceived barriers
Santos (2002)	UK	4282	n/a	n/a	0 hrs 21%; 1 hr 20%; 2-4 hrs 35%; 5-9 hrs 15%; >10 hrs 9%	Sport, AS specific HEP or hydrotherapy	2-4 hrs/ week positively associated with function & inversely associated with dis. act. >10 hrs improved function but not dis. act.
Sundstrom (2002)	Sweden	189	Daily 9%; 3-6 x/week 15%; 1-2 x/week 30%; <1x/week 26%; no exs 17%	n/a	n/a	Walk 57%; pool exs 38%; cycle 33%	Most common exercise barriers were lack of time and fatigue
Uhrin (2000)	USA	220	Back exercises: 30% 0 days/week; 40% 1-4 days/week; 11% 5-7 days/week	n/a	Median PAL 85 mins/week	Back exs Rec exs – several listed	Back exs> 5days/week & rec. exs > 200 mins/week associated with decrease in pain & stiffness, improvement in function
Ward (2002)	USA	212	Back exs 3±2.6 days/week	n/a	Rec. exs. 139 ± 161 mins/week	Back exs Rec exs – several listed	More frequent back exs associated with slower progress of functional disability over 5 years

BASDAI Bath Ankylosing Spondylitis Disease Activity Index; dis. act. disease activity; BASFI Bath Ankylosing Spondylitis Functional Index; exs. Exercises; HAQ – Health Assessment Questionnaire ; HEP Home Exercise Program; PAL Physical Activity Level; rec. exs. Recreational exercises; WHO World Health Organisation; IPAQ-SF International Physical Activity Questionnaire Short Form

Table 3.5 Intervention Attributes or Practices that Promote Physical Activity (Adapted from Ruppar [96], with permission)

Strength of Evidence	Attribute or Practice	Definition
Strong	Single target: physical activity only	Interventions designed to modify only behaviour related to physical activity, rather than multiple health behaviours
	Behavioural approaches	Interventions containing at least one behavioural strategy, designed to produce a direct change in behaviour related to physical activity
	Self-monitoring	Interventions including practices such as keeping an activity diary, tracking activity in a calendar, or recording activity on a website
Moderate	Supervised exercise	Exercise overseen by a member of the research team or a health care provider
	Tailoring	Adapting the intervention to meet the needs of the situation or patient
	Contracting	An agreement between patient and provider defining the level and duration of physical activity the patient will perform
	Exercise prescription	Participants receive written instruction for the mode, duration, frequency, intensity and progression of their physical activity
	Fitness testing	Patient's level of physical fitness is evaluated before any physical activity program is initiated
	Stimuli and cues	Interventions employ prompts that remind participants to exercise
	Moderate or high intensity recommendations	Recommendations are for moderate or high intensity (as opposed to low intensity) physical activity

3.10 Appendices

Appendix A Systematic review methods, included and excluded papers

3A1 Systematic Review Methods

3A1.1 Search strategy

- Exercise was defined as: 'the prescription of a physical activity program that involves the client undertaking voluntary muscle contraction and / or body movement with the aim of relieving symptoms or improving function, or improving, retaining or slowing deterioration of health' [1].
- Each member of the working group (WG) independently submitted their ten most important clinical questions about exercise for ankylosing spondylitis (AS). These were grouped according to topic by the project co-ordinators (JM and JZ), and an overarching question was derived for each topic.
- For each clinical question, a systematic review (SR) of five databases (Medline; PEDro; CINAHL; EMBASE; SPORT discus) was undertaken by the main author
- Electronic databases prior to 1/12/12 were searched according to PICO:

Patients	Adults with ankylosing spondylitis (AS) according to modified New York criteria/ rheumatologist diagnosis
Intervention	All therapeutic exercise related interventions
Comparison	No exercise intervention, or a different type of exercise intervention, or usual care
Outcomes	Pain, mobility, disease activity, physical function

- The process was derived from GRADE (Grading of Recommendations, Assessment, Development and Evaluations) Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

- PubMed Search Strategy
    1. "spondylitis, ankylosing" [MESH]
    2. spondyloarth* [all fields]
    3. ankylosi* [all fields]
    4. **1 OR 2 OR 3**
    5. mobil* OR metrology OR range OR movement OR physical
    6. assess* OR measur* OR monitor*
    7. **5 AND 6**
    8. exercis* OR "exercise therapy" OR therap* OR rehabil* OR movement OR motion OR physical OR physio* OR kinesio*
    9. **4 AND 8**
    10. compliance OR adherence OR motivation OR behav* change
    11. "adverse event" OR safety OR harm OR "disease modification" OR "disease progression" OR complication* OR "spinal cord injury" OR fracture
    12. mobil* OR cardio* OR pulmonary OR function OR "quality of life" OR pain OR fatigue OR postur* OR fitness OR range OR metrology
    13. stretch* OR strength* OR mobil* OR resist* OR stabil* OR core OR hydrotherapy OR "posture exercise"
    14. pilates OR tai chi OR aerobic OR swimming OR balneotherapy OR "dance therapy" OR yoga OR walk* OR cycl*
    15. land OR group OR home OR pool OR setting OR facility OR spa OR gym
    16. frequency OR duration OR amount OR dosage OR dos* OR intensity OR prescription OR repetition
    17. **4 AND 7** *[assessment & monitoring]*
    18. **9 AND 10** *[adherence]*
    19. **9 AND 11** *[disease management/ safety]*
    20. **9 AND 12** *[exercise outcome]*
    21. **4 AND 13** *[exercise-AS specific]*
    22. **4 AND 14** *[physical activity]*
    23. **9 AND 15** *[exercise-setting]*

24. 9 AND 16 *[exercise-dosage]*

- The above strategy was modified as required for other databases
- Hand searches of reference lists also completed
- The principle of selecting the best available level of evidence for each topic was applied, and the overarching inclusion and exclusion criteria are shown in Table A1.

3A1.2 Study selection, data extraction and quality assessment

- The WG members were each allocated a selection of randomised trial papers, to review the basis for inclusion (see specific criteria in Table A1) and the evidence quality.
- A pre-determined 'evidence matrix sheet' was completed. It was based on the Physiotherapy Evidence Database (PEDro) scale, which has been shown to have acceptably good reliability [2, 3] and validity [4].
- The PEDro 11 point scale results in a total score out of 10: criterion 1 does not count towards the score. RCTs were rated 'high' quality if they scored 6 or more on the PEDro scale, and those with a score of 5 or less were rated 'low' quality.
- The PEDro scoring criteria are as follows:

    1. Eligibility criteria specified?
    2. Subjects randomly allocated
    3. Allocation concealed?
    4. Groups were similar at baseline?
    5. Blinding of subjects?
    6. Blinding of therapists?
    7. Blinding of assessors?
    8. Outcome measures from >85% of subjects?
    9. Treatment as allocated or as 'intention to treat'?
    10. Statistics presented on between-group analysis for >1 key outcome?
    11. Point measures and measures of variability for >1 key outcome?
    12. Total PEDro score

- Included in the evidence matrix pro forma were the following headings/ questions regarding the reviewer's opinion on the paper:

    1. Provide a summary of study methods and findings
    2. Was the intervention described in sufficient detail to be clinically useful?
    3. What were the strengths of the paper?
    4. What were the limitations of paper?
    5. What is the relevance to the clinical questions for this topic?
    6. Is the intervention readily available in Australia?

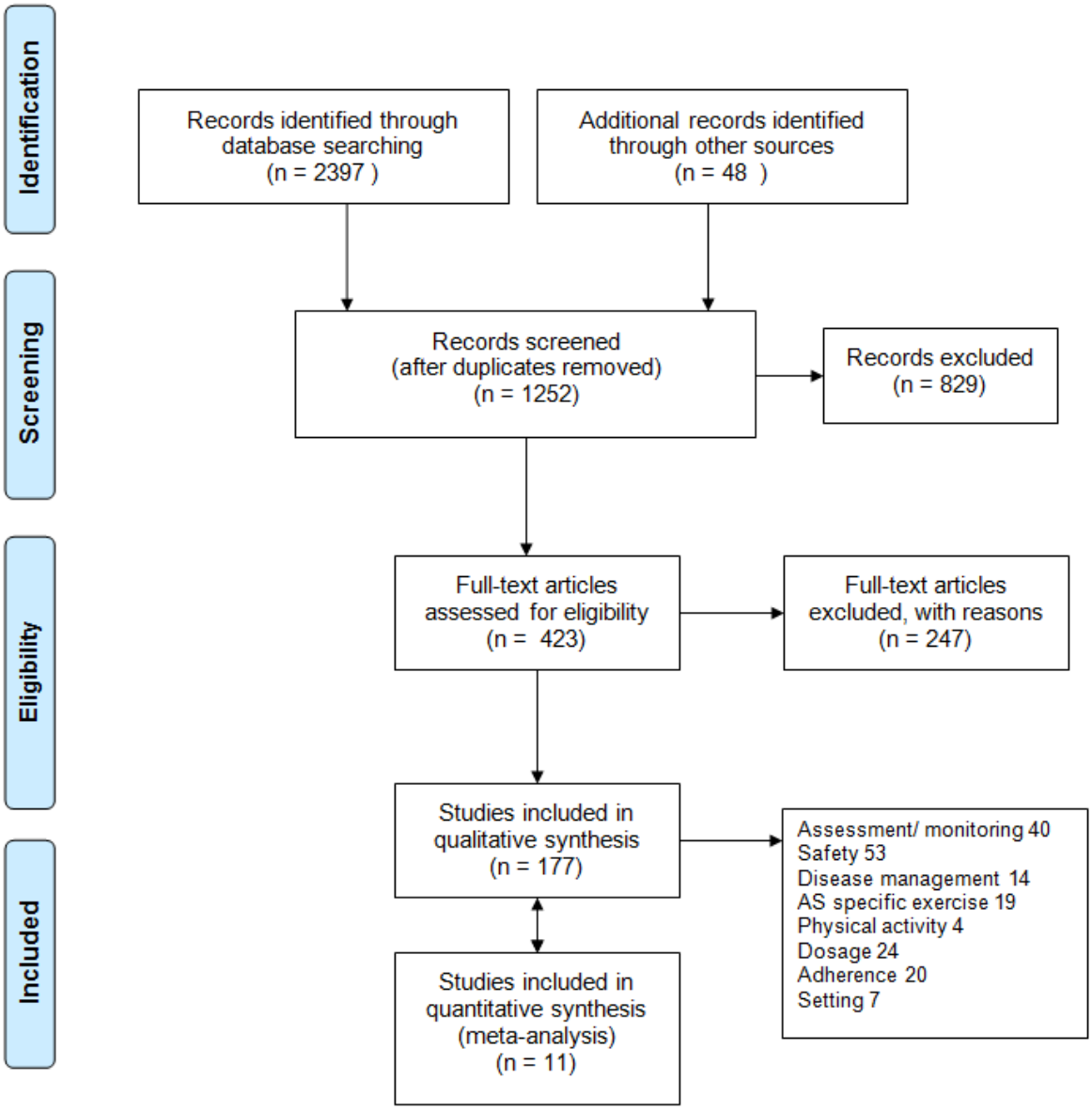
Table 3A1. Overarching inclusion and exclusion criteria

	Inclusion	**Exclusion**
Population	Adults with ankylosing spondylitis (AS) according to modified New York criteria or rheumatologist diagnosis	Participants with other/ unspecified musculoskeletal conditions
Intervention	Subjects participated in active exercise interventions prescribed to manage AS	Exercise was passive only Investigation of interventions other than exercise Provision of exercise information only
Comparison	No exercise, or another type of exercise, or usual advice	
Purpose of paper:	Addresses the clinical question for the topic of interest (i.e. Assessment, Monitoring, Safety, Disease Management, AS-Specific Exercise, Physical Activity, Dosage, Adherence or Setting)	Does not address the clinical question
Outcomes:	Evaluates pain, spinal mobility, disease activity or physical function	Does not address outcomes of interest Evaluation of cost-effectiveness Follow up studies
Type of paper	The highest level of available evidence, according to National Health and Medical Council (NHMRC) guidelines for each topic, i.e. Systematic reviews (SRs) or randomised controlled trials (RCTs) where available	Lower levels of evidence, where SRs and RCTs are available
Language	English	Other languages
Date of publication	Commencement of the database until December 1st, 2012	Publication after 1st December 2012

3A1.3 Data analysis

- Where data were available, we undertook meta-analyses using the Cochrane Collaboration's Review Manager software (RevMan), version 5.2, for outcomes of pain, disease activity, axial mobility and physical function.
- Data were extracted by the main author only, with subsequent review by all authors.
- Mean differences were calculated where the same scale was used for all studies, and standardised mean differences (SMD) calculated where different scales were reported. A random effects model was used due to the heterogeneity of the interventions. We considered heterogeneity of the data statistically significant at $P < 0.1$ by using a standard Chi2 test as well as assessing the I^2 statistic; a value greater than 50% was considered substantial heterogeneity.

Figure 3A1: Search Results



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed10000

3A2 Included Papers

3A2.1 Assessment and monitoring

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3A2.3 Disease management

3A2.3.1 Disease modification

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3A2.4 AS specific exercise

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3A2.7 Adherence

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3A2.8 Setting

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Table 3A3 Excluded Papers

A3.1	
Assessment/ monitoring	
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4. Boonen A, Braun J, van der Horst Bruinsma I, Huang F, Maksymowych WP, Kostanjsek N, et al. ASAS/WHO ICF Core Sets for ankylosing spondylitis (AS): how to classify the impact of AS on functioning and health. Ann Rheum Dis. 2010;69:102-7.	3
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A3.2 **Safety**	
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6. Bessant R, Harris C, Keat A. Audit of the diagnosis, assessment, and treatment of osteoporosis in patients with ankylosing spondylitis. Journal of Rheumatology. 2003;30(4):779-82.	1
7. Casellini C, Citera G, Rosemffet M, Ruggeri S, Saviotti A, Maldonado Cocco JA. Audiovestibular disorders in patients with ankylosing spondylitis. J Clin Rheumatol. 2005;11(2):81-5.	3
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Setting	
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1.Study design did not meet criteria for this topic; 2.Full text article not available; 3.Main aim of study does not address clinical question; 4. Insufficient information provided

3A4 References

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Appendix B: Summary of evidence for recommendations

Table 3B1 Summary for each recommendation

Topic	**3B1.1 Assessment and monitoring**	
Clinical question	***In adults with ankylosing spondylitis (AS), which measures are beneficial for baseline mobility assessment, in order to inform exercise prescription? What are the minimum requirements for monitoring these measures?***	
Criteria	**Inclusion:** Studies include measures related to mobility assessment. Accurately described technique Reproducible in usual clinical setting	**Exclusion:** Mobility measures not well described Not reproducible in usual clinical setting
No & type of studies	40 included papers: 2 – part of RCT; 7 – longitudinal (non-controlled); 9 - cross-sectional (with matched controls); 1 – review; 1 – guideline; 20 – cross-sectional (no controls)	
Level of evidence	Level C/D	
Quality of studies/ risk of bias	n/a	
Relevance to Australian (non-residential) setting	High – large number of studies/ information on physical assessment tools	
Reproducibility of exercises	Accurate descriptions / instructions available for most measures	
Consistency of results	B	
Effect sizes (if applicable)	n/a	
Other factors	No studies were found which directly related choice of assessment/ monitoring tool to exercise prescription	

Recommendation(s)	**Recommendation 1: Assessment** ***Individual assessment prescription should be informed by a thorough and reproducible assessment which includes musculoskeletal and psychosocial factors, and AS-specific measures -including objective axial mobility and chest expansion.*** **Recommendation 2: Monitoring** ***Sufficient monitoring and feedback should be provided on an individual basis, to achieve confidence and competence with exercise, and to inform changing needs for exercise prescription. This is recommended at least annually, and more often as symptoms, function and mobility indicate.***
Grading of Recommendation(s)	**Recommendation 1: CBR** • Despite the large number of studies regarding assessment methodology for AS, no direct evidence was found which answered the clinical question. • The information obtained regarding assessment methods has been summarised as practice points for recommendations 1 and 2. **Recommendation 2: CBR** • No direct evidence on minimum monitoring requirements was found • Some evidence was found linking exercise adherence with monitoring of mobility measures (refer to Topic 9-adherence).

Discussion	Most (29) studies were cross-sectional and most (27) did not include controls. Reviews by the Assessment of SpondyloArthritis International Society (ASAS) [1, 2] resulted in a recommended 'core set' of individual spinal mobility measures, which are incorporated in two composite AS anthropometric measures, the Bath AS Metrology Index (BASMI) [3] and the Edmonton AS Metrology Index (EDASMI) [4]. Each has advantages and limitations, as outlined in the practice points, however, both fulfil the requirement for a validated, easily reproducible tool, which can provide clinical guidance on exercise choice for individual patients. Chest expansion is a measure of thoracic mobility but the WG also questioned whether it could indicate cardiorespiratory function (CRF). Ten studies were found which investigated the associations between anthropometic measures, such as chest expansion, and laboratory measured CPF. Two small cross-sectional studies [5, 6] did not find such an association, but the remainder did, including a larger cross-sectional, controlled study with 147 patients with AS and 121 controls. This demonstrated a 'clear relationship' between reduced spinal mobility (including chest expansion) and restrictive pulmonary function in subjects with AS [7]. Given the importance of thoracic mobility and CRF, monitoring of chest expansion is therefore a recommended baseline measure. No direct evidence was found to inform frequency of monitoring of anthropometric and other measures. However, since AS is a progressive condition, and optimal exercise recommendations vary over time, longitudinal repetition of physical measures to inform adjustment to individual prescription makes clinical sense.

Topic	**3B1.2 Safety**	
Clinical question	***In adults with AS, what safety aspects should be considered in relation to exercise prescription?***	
Criteria	**Inclusion:** Studies include aspects which could influence safety in exercise prescription, i.e. balance; cardio-vascular & pulmonary function, fracture risk/ osteoporosis Full text articles Experimental studies and reviews Guidelines for other chronic conditions (where no direct evidence available)	**Exclusion:** Case studies Conference abstracts only
No & type of studies	53 included papers: 17 - cross-sectional (with matched controls); 11 – cross-sectional (no controls); 18 – review; 3 – systematic review; 1- case series; 3- guidelines addressing broader groups (chronic disease, osteoporosis, pre exercise screening)	
Level of evidence	Level C/D	
Quality of studies/ risk of bias	n/a	
Relevance to Australian setting	High – large amount of information on disease consequences	
Reproducibility of exercises	n/a	
Consistency of results	B	
Effect sizes (if applicable)	n/a	
Other factors	No studies were found which directly related to safety in exercise prescription. Broader information on aspects known to influence exercise safety was therefore sought.	

Recommendation(s)	**Recommendation 3: Safety** ***Throughout all aspects of exercise prescription, especially for those with more severe or later disease, the physical changes of AS must be considered. These include the amount of bony change/ ankylosis, balance and mobility changes, osteoporosis, and cardio-pulmonary consequences of the disease (CBR)***
Grading of Recommendation(s)	**Recommendation 3: CBR** • No direct evidence was found which answered the clinical question, therefore graded CBR • There is considerable evidence regarding known exercise risk factors such as cardio-pulmonary impairment, osteoporosis and balance impairment in AS • Although adverse events for exercise in AS have not been reported, there is anecdotal evidence within the group of such occurrences. This has been incorporated into the practice points.
Discussion	For people with more severe disease, the task of planning exercise that is simultaneously effective in terms of training [8] but minimises the risk of an adverse event, requires an appropriate level of knowledge, skill and planning. The evidence underscores the importance of adequate assessment prior to commencement of an exercise program, and monitoring of outcomes. BASMI and chest expansion, in conjunction with imaging findings, may help guide the level of structural change and potential risk. Standard exercise guidelines may require significant modification for an individual with ankylosis, in terms of type of exercise, starting position, baseline intensity and grading of progression [9], as indicated in the practice points. These are in addition to the pre-exercise screening that is recommended for all adults prior to an increase in aerobic exercise levels [10]. Reference to other guidelines for exercise prescription in chronic disease, [11] or osteoporosis [12] may also be indicated.

Topic	**3B1.3 Disease Management**	
Clinical questions	***(a) In adults with AS, is exercise effective in disease modification (reduction in progression), compared with no exercise?*** ***(b) In adults with ankylosing spondylitis, are exercises in combination with anti-TNFα medication more beneficial (for pain/ function/ disease activity/ mobility) than medication alone?***	
Criteria	**Inclusion:** (a) Experimental studies of any design (b) Studies comparing exercise + anti-TNFα medication combinations with medication alone	**Exclusion:** Case studies
No & type of studies	(a) 8 included papers: 1 – RCT; 2 – non-random experimental trials; 1 – interrupted time series without control group; 1- cross-sectional (no controls); 1- case control study; 1 – case series; 1 - review (b) 6 included papers: 2 – RCT (only 1 full article); 2 – non-random experimental trials; 2 – interrupted time series without control group	
Level of evidence	(a) Level C – several Level 111-3 studies (b) Level B – one RCT and several level 11 studies	
Quality of studies/ risk of bias	(a) 1x RCT (abstract only, unable to rate quality) (b) 1x high quality RCT (PEDro 7/10), i.e. low risk of bias; 1x RCT with low PEDro score (5/10), i.e. high risk of bias	
Relevance to Australian setting	(a) Highly relevant – there can be clinical concern about increasing disease activity with exercise (b) Highly relevant – anti-TNFα medication is widely used; exercise interventions used similar to those available	
Reproducibility of exercises	Well described in Masiero paper [13]	
Consistency of results	(a) Level C: The evidence suggests that exercise could influence both self-reported disease activity and physiological inflammatory markers, however, the direction of effect is conflicting. (b) Level A: Small number of papers/ subjects but direction of results appears consistent for function, disease activity, mobility and pain	

Effect sizes (if applicable)	(Exercise and anti-TNFα medication) Standardised mean differences for anti-TNFα + exercise versus anti-TNFα + no exercise (Masiero): pain 0.63; mobility 0.29-0.42 and physical function 0.56 in favour of anti-TNFα + exercise. Mean differences of 0.56 (Bath AS Disease Activity scale) and 0.95 cm chest expansion in favour of exercise.
Recommendation	**Recommendation 4: Disease Management** ***Individuals receiving anti-TNFα therapy should continue with regular exercise prescription as it confers an additional benefit to anti-TNFα therapy alone. (EBR, grade B)***
Grading of Recommendation and Rationale	**EBR - Level B** (a) No recommendation could be made regarding disease modification due to uncertainty around this issue. (b) Exercise in combination with an anti-TNFα medication, and anti-TNFα medication without exercise, were directly compared in a small number of studies. One high quality RCT found significant benefits for the anti-TNFα / exercise combination. This finding was supported by 5 lower quality studies and by the experience of the writing group.
Discussion	(a) Seven small studies were found investigating the effects of exercise on markers for inflammatory disease activity, with conflicting results. One RCT [14] and one non-controlled interrupted time series [15] found no change in cytokine levels with aerobic exercise or a multi-modal program respectively. However, a number of other observational studies did find statistically significant increases in anti-inflammatory cytokines following exercise [16-19]. No studies were found which examined potential local effects of stretch or mobility exercise on entheses or soft tissues. Despite consistent findings that exercise is effective in AS, the potential interactions between the physiological effects of exercise and the pathological processes have yet to be clarified. Although there are more studies demonstrating a trend towards mediation of inflammation, there is no definitive evidence for whether exercise produces local effects (for example, at the enthesis) or systemically, that is, a general anti-inflammatory effect, and so no recommendation was made. (b) The best quality trial was by Masiero [13], who investigated three groups of patients already stabilised on an anti-TNFα medication: one received education; another education plus an out-patient based multi-modal exercise program, and the third was a control group. The study design was a single-blinded, randomised controlled trial, with a PEDro score of 7/10 and 'high' scores for reproducibility and relevance. Both intervention groups had improved BASFI and pain levels at 3 and 6 months, but the combination with exercise also had statistically significant improvements in BASMI, chest expansion and quality of life.

Topic	**3B1.4 AS-Specific Exercise**	
Key question	***In adults with AS, is therapeutic (specifically prescribed) exercise aimed at*** ***(a) improving mobility/ posture*** ***(b) increasing strength*** ***(c) improving cardiorespiratory fitness*** ***(d) improving function (balance, co-ordination, gait, agility and proprioception)*** ***more beneficial for pain, mobility, disease activity and physical function than no exercise/ general advice only?***	
Criteria	**Inclusion:** Systematic reviews or RCTs Investigation of AS-Specific (therapeutic/ prescribed) exercise Full text articles Intervention widely available and / or reproducible in Australia Primary aim is trial of therapeutic benefit Outcome measures: mobility, pain, disease activity, function	**Exclusion:** Case studies Conference abstracts only General physical activities not specifically adapted for AS Descriptive/ opinion papers Primary aim is to investigate cost effectiveness/ adherence
No & type of studies	19 included papers: 11 x RCTs (6 included in Cochrane Review 'Physiotherapy interventions for ankylosing spondylitis' 2008; 5 RCTs post-Cochrane) 7 x SRs (3 with meta-analysis) 1x overview of exercise SRs including AS	
Level of evidence	A	

Quality of studies/ risk of bias	RCTs of mixed quality and small-moderate size; issues of heterogeneity between studies with regard to type of intervention, measurement points, measures; PEDro scores for included RCTs: 7/10 x 5; 6/10 x 4; 5/10 x 1; 4/10 x 1. In general there was a lack of reporting regarding exercise program design, assessment and outcome measurement for physiological effectiveness. **See table B1 for RCTs rated by PEDro criteria.** No studies met the criteria for blinding of subjects or therapists: however, this is rarely feasible with exercise interventions. The other criterion that was largely unmet was intention to treat analysis, which was generally not specified, and a potential reason for bias. Each intervention arm typically included around 20 participants, with the duration of exercise programs varying from six to 36 weeks. Six studies compared experimental exercises with no exercise or information only, whilst five compared two different exercise interventions. Of the outcomes of interest, physical function was reported in nine studies, disease activity in seven and pain in only five studies. All studies performed at least one mobility measure, but measures chosen varied in both type and methodology. Only three studies utilised the Bath Ankylosing Spondylitis Metrology Index (BASMI), and none used the more sensitive BASMI 10 point scale, so calculation of mean differences for a composite mobility measure was not possible. Therefore the four most widely reported measures were chosen for further analysis: cervical mobility (calculated as standardised mean difference (SMD)); finger to floor distance (calculated as mean difference (MD) in centimetres (cm)), chest expansion (MD, cm) and lumbar flexion (SMD).
Relevance to Australian setting	11 trials were considered highly relevant; 6 RCTs excluded due to low relevance (e.g. spa or in-patient treatment). The only high quality RCT comparing two types of flexibility exercise in AS was that of Fernandez [20], who found benefits for Global Posture Re-education (GPR), a method mainly practiced in Europe, which targets shortened muscle trains with a series of whole-body stretching and strengthening exercises, compared with a series of static stretches. The use of this technique is not known to the WG. However, the techniques as described appear similar to other dynamic mobility and static stretch exercises, although with perhaps higher repetitions for the former and longer stretch times for the latter, than might commonly be practised in Australia.
Reproducibility of exercises	RCTs mainly provided sufficient information to reproduce exercises in the clinic, except Cagliyan 2007. Where exercises were adequately described, they were a combination of dynamic flexibility, static and dynamic stretches, with no RCTs examining ballistic stretches. A number of RCTs included strengthening exercises as part of 'multi-modal' programs [13, 20-23], but no strength outcome measures were reported, and descriptions of the use of weights or other forms of resisted exercise were not found in the included studies.
Consistency of results	Highly consistent; no studies found which resulted in a negative outcome for exercise interventions

Effect sizes (if applicable)	Dagfinrud et al performed a meta-analysis of 11 RCTS or quasi randomised trials, published prior to January 2007, with a total of 763 participants, the outcome measures being: pain; stiffness; axial mobility; physical function and patient global assessment. Pair-wise comparisons were made for different modes of delivery (individualised home exercise program (HEP), supervised or group exercises) and different settings ("dry land", spa, balneotherapy and fresh water pool exercises). One comparison was made between different exercise *types* ('Global Postural Re-education versus a 'conventional' mobility and stretch program). The results were reported in relative percentage differences (RPDs), with ranges of: 5-50% favouring a structured exercise program (HEP or supervised) over none for mobility, and 7.5-18% favouring groups over HEPs. From our meta-analyses, effect sizes [confidence intervals] for included RCTs were all in favour of interventional groups as follows: pain SMD -0.42[-0.74, -0.09]; disease activity (BASDAI score) MD -0.47[-0.84,-0.09]; cervical mobility SMD 0.20[-0.09,0.49]; fingertip to floor distance (MD, cm) -4.87[-8.38,-1.37]; chest expansion (MD, cm) 0.81[0.35,1.28]; lumbar flexion (SMD) 0.35[0.02,0.67] and physical function (SMD) -0.51 [-0.81,-0.21].
Other factors	See Forest plots (figure 2 in main text). There was moderate ($I^{2=}$26%) statistical trial heterogeneity for lumbar flexion and substantial (I^2=62%) heterogeneity for physical function. The reasons for this are unclear but may include methodological differences in exercise intervention studies, particularly exercise programme design and dosage attained.
Recommendation(s)	**Recommendation 5: AS-Specific Exercise (Mobility)** **Individual exercise prescription with an emphasis on spinal mobility is paramount for best management of AS. Maintaining mobility of peripheral joints is also essential. This can be achieved through a number of approaches. At this time we are unable to recommend one approach over another, therefore individual goals should be informed by assessment findings. *(EBR, grade A).*** **Recommendation 6: AS-Specific Exercise (Other)** ***Stretching, strengthening, cardiopulmonary and functional fitness are important components to consider in a balanced exercise program (EBR grade B)***
Grading of Recommendation(s)	• Systematic reviews and a moderate number of RCTs • Findings supported by international consensus and experience of the WG • Recommendation 6 downgraded from grade A due to the indirect nature of some of the evidence, i.e. extrapolated from the healthy adult/ chronic disease literature.

Discussion	Exercises described in papers or in patient-directed resources, such as those produced by the UK National Ankylosing Spondylitis Society publication 'Back to Action' (http://nass.co.uk/exercise/exercise-for-your-as/back-to-action/) typically include combination of soft tissue stretch and dynamic joint mobility exercises for 'tight' or shortened soft tissues/ restricted joints, in conjunction with strengthening of 'lengthened' muscles. . The WG was interested in whether specifically prescribed, therapeutic exercises, were more beneficial for pain, physical function, disease activity and axial mobility, than no exercise or general exercise advice only. In the 2009 Cochrane review of Physiotherapy interventions for ankylosing spondylitis [24] found 'Silver' level evidence (RCTs with less than 50 subjects per group) that: individual or home-based exercises are beneficial; that supervised group physiotherapy has additional benefit over home exercise, and that combined spa-exercise therapy was more beneficial than group physiotherapy alone. Meta-analysis was also performed in a 2012 ASAS/EULAR update of non-pharmacological recommendations for AS management [25], and the findings supported the positive trend for exercise effectiveness in AS. Cohen's effect sizes (ES) were found to be beneficial in a small to moderate range for self-reported pain, disease activity and physical function, and objective axial mobility, although in a number of studies statistical significance was not reached. However, most of the included studies in this paper investigated balneotherapy, which is not widely available in Australia (and thus excluded from our analysis) and four of the nine included studies were of low quality according to the PEDro scale. In a 2011 paper, Dagfinrud et al analysed the reported components of the exercise programs used in twelve previous RCTs, assessing program design and outcomes against American College of Sports Medicine (ACSM) criteria [8]. This study had similar findings regarding effectiveness, with positive effect sizes of 0.14-0.67 for mobility. All the reviewers commented on the difficulties of extracting meaningful data, due to small sample sizes, heterogeneity of exercise interventions (exercise type, dosage and trial duration) and outcome measures. The Cochrane review [24] also noted that most studies (7 out of 11) compared two similar exercise interventions, therefore between-group differences (unsurprisingly) could not be proved. However, the results were very consistent for small to moderate positive effects for exercise in the parameters measured. **(a) Mobility (flexibility) exercise** Shortfalls were found in both the descriptions of exercises used and outcome measures. Where exercises were adequately described, they were a combination of dynamic flexibility, static and dynamic stretches, with no RCTs examined ballistic stretches. The only high quality RCT comparing two types of flexibility exercise in AS was that of Fernandez [20], who found benefits for Global Posture Re-education (GPR). **(b) Strengthening exercises** have received little attention in the AS literature: despite the large body of evidence demonstrating benefits for bone, cardiovascular health and prevention of falls in healthy adults [26, 27]. A number of RCTs included strengthening exercises as part of 'multi-modal' programs [13, 20-23], but no strength outcome measures have been

	reported, and descriptions of the use of weights or other forms of resisted exercise were not found in the included studies. Indirect evidence suggesting potential benefits in individuals with AS includes controlled cross-sectional studies showing: diminished muscle strength compared with matched controls [28-30]; a mild to moderate decrease in vital capacity in association with peripheral muscle strength [5] and an association of upper extremity strength with spinal mobility [31]. Finally, the biomechanical principles of muscle balance, that is, the maintenance of relative equality of muscle strength/ length between antagonist and agonist [32] would suggest strengthening exercise should be part of a balanced exercise program. **(c) Cardiorespiratory exercise** training was included in five high quality RCTs of multi-modal programs designed for AS [13, 21, 23, 33, 34]. Dagfinrud [8] compared effect sizes for aerobic capacity, with exercise program design relative to ACSM guidelines for physical activity levels in healthy adults. The ES ranged from 0.09 (for an in-patient multi-modal exercise program) to 2.19 (for an out-patient multi-modal program). The highest ES for aerobic capacity [33] was in the only study where the exercise dosage tested met the ACSM guidelines, and Dagfinrud concluded that most study programs are physiologically ineffective, highlighting the importance of appropriate exercise program design for effectiveness. One study [34] specifically targeted pulmonary function by testing an intensive (30 minutes per day for 16 weeks) regime of incentive spirometer (IC) use in addition to conventional exercises (CE). In comparison to CE alone, there were significant improvements in vital capacity with the IC method. **(d) Functional (neuromotor) exercise** can include motor skills such as balance, co-ordination, gait, agility and proprioceptive training, as well as re-education of motor control for specific muscle groups. Regular performance is recommended by the ACSM [35] and as part of the national physical activity recommendations for older Australians [36], and they gain relevance for individuals who have impaired balance and gait/ movement compensations due to spinal ankylosis. Despite the absence of RCTs investigating balance or other neuromotor interventional measures in AS, the indirect evidence and WG's experience supports the inclusion of this group of exercises.

Table 3B2 RCT quality assessed by Physiotherapy Evidence Database (PEDro) criteria

Criterion	Eligibility Criteria specified *	Random allocation	Concealed allocation	Baseline comparability	Blinding of subjects	Blinding of therapists	Blinding of assessors	Adequate follow up	Intention to treat analysis	Between group comparisons	Point estimates/ variability	Total Score/ 10
Altan 2012	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Analay 2003	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Cagliyan 2007	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Fernandez-Penas 2005	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Hidding 1993	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Ince 2006	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Kraag 1990	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Lee 2008	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	6
Lim 2005	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Masiero 2011	Yes	Yes	Yes	Yes	No	no	Yes	Yes	No	Yes	Yes	7
So 2012	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6

* Eligibility Criteria does not contribute to total score

Topic	**B1.5 Physical Activity**	
Clinical question	***In adults with AS, what types of physical activity are beneficial for pain, mobility, disease activity and function?***	
Criteria	**Inclusion:** SRs/ RCTs pertinent to clinical question Investigate exercise available to general population (may be modified for AS) Full text article	**Exclusion:** Descriptive/ opinion papers
No & type of studies	3 - RCTs; 1 - large case series (1538 subjects) A small RCT by Lee et al in 2007 [37] had 20 subjects and controls, a PEDro score or 6/10, and demonstrated improved BASDAI and fingertip to floor distance following an eight week tai chi program. A larger study, with 30 subjects and a PEDro score of 8/10, showed significant improvements in BASMI, BASDAI and chest expansion following three x one hour sessions of Pilates training for 12 weeks. Both studies used programs that were somewhat adapted for the research protocol, so these findings should be used with caution when considering 'mainstream' tai chi or Pilates programs. Swimming is commonly recommended for AS, but only one low quality (PEDro rating 5/10) study was found for this activity [38]. A comparison of swimming, walking and conventional exercises over six weeks demonstrated a range of benefits for all three groups; however, swimming was statistically superior for disease activity (BASDAI) and six minute walk test. Falkenbach' s cross-sectional study of 1538 patients showed an association between PALs and mobility, but no significant differences were found between types of leisure activities/ sports [39]. There is an extensive body of background evidence for national physical activity guideline development [26, 27].	
Level of evidence	Direct evidence (AS subjects) – Level B Indirect evidence (population based) – Level A	
Quality of studies/ risk of bias	2x high quality (PEDro score 6/10 & 8/10); 1 x low quality (PEDro score 5/10) RCTs	
Relevance to Australian setting	High – the physical activities studied are widely available (swimming, walking, tai chi, Pilates)	

Reproducibility of exercises	n/a
Consistency of results	B – all activities showed some benefit, with variation among effect sizes
Effect sizes (if applicable)	Small effect sizes (in favour of physical activity intervention) for outcomes of interest: • Pilates: Bath AS Disease Activity Index (BASDAI) -0.16; physical function SMD -0.36; chest expansion 0.5 cm • Tai chi: BASDAI -0.76; finger to floor distance 0.5cm • Swimming: BASMI SMD 0.27; Schober test -0.09 cm Data from Dagfinrud (2011) [8]
Other factors	The number of potentially beneficial physical activities studied was small
Recommendation(s)	Recommendation 7: Physical Activity (EBR, grade B) Regular physical activity should be encouraged to promote general health, well-being and functional outcomes.
Grading of Recommendation(s)	**Recommendation 7: EBR, grade B** • Large/ consistent body of high level evidence for the general population • There is no reason for the benefits for maintaining health/ preventing disease not to be applicable for people with AS • Recommendation has been down-graded from A due to small number of studies with subjects who have AS.

Topic	**B1.6 Dosage**	
Key question	***In adults with AS, what dosage of exercise is beneficial for pain, mobility, disease activity and function?***	
Criteria	Inclusion: Subjects with AS Any research design Full text or abstract Addresses clinical question (compares quantity of exercise with outcome measures)	Exclusion: Case studies
No & type of studies	Exercise volume in RCTs – 11 Habitual exercise volume 13 included papers: 3 – cross-sectional studies; 6 – patient surveys; 4 – case series	
Level of evidence	Level C	
Quality of studies/ risk of bias	RCT PEDro scores: 7/10 x 5; 6/10 x 4; 5/10 x 1; 4/10 x 1. Surveys were all self-reports (except Arends 2011) and varied in number of subjects, from 50 to 4282.	
Relevance to Australian setting	High – studies completed in Europe/ USA/ Canada – however, there is nothing to suggest that exercise response would be different in Australians	
Reproducibility of exercises	Exercise intensity was only reported in 45% of studies. Exercise time was frequently totalled into a weekly amount, with the range being 60 to 700 minutes per week and 30 to 60 minute sessions being typical. In general, the exercise dosage for different components of multi-modal programs was not specified. Further limitations were the reliance on self-reported exercise dosage for home exercise programs, and the lack of information on progression of exercise dosage.	
Consistency of results	B – Studies consistently showed benefit across a range of measures, although there was variation in volume of exercise dosage and benefit	
Effect sizes (if applicable)	n/a	

Other factors	
Recommendation(s)	**Recommendation 8: Dosage** **Exercise frequency, intensity, duration and type must be tailored to the person's assessment findings, goals and lifestyle.** **(a) For mobility, stretch & postural exercise, consistency is the most important factor** **(b) For other exercise types, national physical activity guidelines may require modification. Consideration should be given to disease stage, activity & progression, whilst aiming for optimal effectiveness**.
Grading of Recommendation and Rationale	**Recommendation 8: EBR, grade C** • Dosage for AS-specific exercise is unclear, although frequency and consistency appear to be the most important factors. • A wide variation was found in dosage used in clinical trials and in self-reported habitual exercise. A large number of factors impact on a person's exercise response, therefore individual tailoring is recommended. However, the body of AS research and nationally recommended physical activity levels for healthy adults can provide some clinical guidance. • There is a large volume of high level evidence for physical activity levels and emerging evidence for anti-inflammatory effects of exercise in healthy adults.
Discussion	The 2011-12 Australian Health Survey indicated that 57% of adults did not meet the Australian National Physical Activity Guidelines for adults [40]. There are similar findings in the Americas and Europe, and this has prompted increased research attention on population adherence to physical activity recommendations. A review of this literature is beyond the scope of this paper, but is well summarised in publications such as the ACSM's Guidelines for Exercise Testing and Prescription [41].

Topic	**B1.7 Adherence**	
Key question	***In adults with AS, which interventions are beneficial for supporting adherence to an exercise plan?***	
Criteria	Inclusion: Any research design Full text or abstract Addresses clinical question SR of PALS in chronic conditions	Exclusion: Clinical question not addressed Case studies Small studies <10 subjects
No & type of studies	(Subjects with AS) 20 included papers: 1 – RCT; 1 – non-randomised trial; 7 – cross-sectional (no controls); 2 – qualitative studies; 1- retrospective cohort; 1- case series; 3 - surveys (Subjects with arthritis/ chronic condition): 4 - SR	
Level of evidence	Direct evidence (subjects with AS) – C (level 111 studies) Indirect evidence (subjects with arthritis/ chronic conditions) – A (level 1 studies)	
Quality of studies/ risk of bias	Direct evidence - PEDro score for RCT – 7/10	
Relevance to Australian setting	High – Physical Activity literature suggests adherence issues are similar in industrialised countries	
Reproducibility of exercises	n/a	
Consistency of results	B – Heterogeneity in size of effect for improving exercise adherence	
Effect sizes (if applicable)	n/a	
Other factors	Limited evidence of mixed methodology was obtained for subjects with AS, so the search was broadened to include SRs for chronic conditions	

Recommendation(s)	Recommendation 9: Adherence It is important to assess adherence with regular exercise, encourage motivation and promote ongoing self-management. (EBR, grade B)
Grading of Recommendation(s) and Rationale	**Recommendation 10: CBR** • There is no reason for the findings regarding exercise adherence in chronic conditions not to apply to AS, therefore the level of evidence has been upgraded from C to B
Discussion	Surveys typically found that approximately one third of people with AS reported meeting previously recommended guidelines for exercise. Differentiation between therapeutic exercise (performed specifically for AS) and recreational or other forms of physical activity was lacking. Nevertheless, it appears that, similar the most developed populations, adherence to exercise recommendations is an area where there is large potential for improvement. It has been suggested that having an arthritis diagnosis may be a prompt to perform habitual exercise for some, but a barrier for others, [42], and in the experience of the WG this also applies to people with AS.

Topic	**B1.8 Exercise Setting**	
Key question	***In adults with AS, which widely available exercise settings and modes of delivery are beneficial for pain, mobility, disease activity and function?***	
Criteria	**Inclusion:** Systematic reviews with MA RCTs since Jan 2007 (date of Cochrane r/v) Full text articles Compares 2 settings Setting widely available	**Exclusion:** Descriptive/ opinion papers Included in Cochrane review Setting not widely available (e.g. in-patient, spa)
No & type of studies	7 included papers: 3 – SR with meta-analysis; 4 - RCT	
Level of evidence	B	
Quality of studies/ risk of bias	2 - RCTs of high quality (PEDro score ≥ 6/10); 2 – RCTs of low quality (PEDro score ≤ 5/10)	
Relevance to Australian setting	Significant proportion of RCTs excluded as setting not widely available	
Reproducibility of exercises	Interventions were adequately described for reproduction in clinic	
Consistency of results	B – Most results consistent, although one (non-randomised) study did not find additional benefit for group over home exercise	
Effect sizes (if applicable)	See AS specific section	
Other factors	Wide heterogeneity of interventions in balneotherapy studies mean that it is not possible to determine what effects may be due to the active exercise components	
Recommendation(s)	**Recommendation 10: Exercise Setting** ***Priority should be given to patient preference in exercise choice, to enhance adherence and optimise positive outcomes***	

Grading of Recommendation(s)	**Recommendation 10: CBR** • Many studies investigated exercise settings not readily available, particularly on a long-term basis (e.g. spa/ in-patient treatment) • Effect sizes for studies investigating different settings were often small. It is not clear whether the type of exercise or the setting in which it is performed are of most importance. However, since exercise is only effective with ongoing performance, personal preference for exercise setting was considered by the group to be the highest priority. • There is limited evidence for superior results with supervised group sessions and / or pool based exercise, however, WG experience is favourable for these settings.
Discussion	Since the Cochrane review (publications to January 2007) [24], a further four RCTs have been published which meet the criteria for this topic. One small lower-quality RCT compared the same exercise program performed at home or in an out-patient group setting twice per week, finding small improvements in BASDAI and BASFI for the group, but no significant difference in BASMI [43]. A short-term (six week) study of swimming and a home exercise program (HEP), walking and HEP or HEP alone, resulted in a statistically significant improvement in mobility (BASMI), QoL and pulmonary function (vital capacity) measures, with additional gains in maximal oxygen consumption (pVO2) and six minute walk test for the walkers and swimmers [38]. Two more recent studies have compared out-patient group rehabilitation [13] and group Pilates [44] to no active intervention. These higher quality RCTs (rated 7/10 and 8/10 on the PEDro scale) both demonstrated significant improvements in mobility (BASMI and chest expansion) and disease activity (BASDAI). No RCTs demonstrating a negative effect for exercise intervention in any setting were found.

Table 3B3 Key to Evidence Summaries [45]: Adapted from Australian Government National Health and Medical Research Council (NHMRC) additional levels of evidence and grades for recommendations for developers of guidelines [46]

Level of Evidence	A	One or more level 1 studies with a low risk of bias or several level 11 studies with a low risk of bias
	B	One or two level 11 studies with a low risk of bias, or SR/ several Level 111 studies with a low risk of bias
	C	One or two Level 111 studies with a low risk of bias, or Level 1 or 11 studies with a moderate risk of bias
	D	Level 1V studies or Level 1 to 111 studies / SRs with a high risk of bias
Quality of studies/ risk of bias	For RCTs, Physiotherapy Evidence Database (PEDro) score [47] (scoring ≥6 for High, 5 or less for Low)	
Relevance to Australian setting	Reviewer's opinion. Scored as High (directly relevant to Australian health care setting) or Low (not directly relevant to Australian health care setting)	
Reproducibility of exercises	Scored as Yes or No. Reviewer's opinion of whether intervention could be reproduced, based on description in study methodology	
Consistency of results	A	All studies consistent
	B	Most studies consistent, and inconsistency may be explained
	C	Some inconsistency, reflecting genuine uncertainty around clinical question
	D	Evidence is inconsistent
Effect sizes (if applicable)	Mean differences where estimable (i.e. same outcome measures used); standardised mean differences (Cohen's d) where outcome measure varied	

Other factors	Any other factors considered by the group, which may upgrade/ downgrade the recommendation	
Grade of recommendation(s)	**Evidence Based Recommendation (EBR)** Based on body of evidence. A recommendation cannot be graded A or B unless the levels of evidence (types of studies) and consistency of results are both graded A or B.	
	A	Body of evidence can be trusted to guide clinical practice
	B	Body of evidence can be trusted to guide clinical practice in most situations
	C	Body of evidence provides some support for recommendation(s), but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	Consensus-based recommendation (CBR): developed by the writing group (WG) when a systematic review of the evidence found either an absence of direct evidence which answered the question, or poor quality evidence, not strong enough to form an EBR. **Practice Points (PP):** developed by the WG where there was a need to provide practical guidance to support the implementation of the EBRs and/or CBRs.	

Table 3B4 Designation of Levels of Evidence (NHMRC Evidence Hierarchy)

Level	Intervention	Aetiology
1	A systematic review of randomised controlled trials	A systematic review of level 11 studies
11	A randomised controlled trial	A randomised controlled trial
111-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
111-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series within a parallel control group	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study
111-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
1V	Case series with either post-test or pre-test / post-test outcomes	Case series

B4 Study Types, as defined by NHMRC

Case-control study – people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/ non-exposure to the intervention or factor under study.

Case series – a single group of people exposed to the intervention (factor under study). **Post-test** – only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. **Pre-test/ post-test** – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared.

Cohort study – outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed.

Prospective cohort study – where groups of people (cohorts) are observed at a point in time to be exposed or not exposed to an intervention (or the factor under study) and are then followed with further outcomes recorded as they happen. **Retrospective cohort study** – where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, e.g. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.

Cross-sectional study – a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time i.e. proportion of people with asthma in October 2004. This type of study is useful for hypothesis-generation, to identify whether a risk factor is associated with a certain type of outcome, but more often than not (except when the exposure and outcome are stable e.g. genetic mutation and certain clinical symptoms) the causal link cannot be proven unless a time dimension is included.

Historical control study – outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (i.e. control group/usual care), or (2) the outcomes of a previously published series of people undergoing

the alternate or control intervention.

Interrupted time series with a control group – trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention (factor under study).

Interrupted time series without a parallel control group – trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and compared (as opposed to being compared to an external control group).

Non-randomised, experimental trial - the unit of experimentation (e.g. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared.
This can include: (1) **a controlled before-and-after study**, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group. (2) **an adjusted indirect comparison**, where two randomised controlled trials compare different interventions to the same comparator i.e. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.

Pseudo-randomised controlled trial - the unit of experimentation (e.g. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.

Randomised controlled trial – the unit of experimentation (e.g. people, or a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared. Cross-over randomised controlled trials – where the people in the trial receive one intervention and then cross-over to receive the alternate intervention at a point in time – are considered to be the same level of evidence as a randomised controlled trial, although appraisal of these trials would need to be

tailored to address the risk of bias specific to cross-over trials.

Systematic review – systematic location, appraisal and synthesis of evidence from scientific studies.

Two or more single arm study – the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared. *Also see entry on unadjusted indirect comparisons.*

Unadjusted indirect comparisons – an unadjusted indirect comparison compares single arms from two or more interventions from two or more separate studies via the use of a common reference i.e. A versus B and B versus C allows a comparison of A versus C but there is no statistical adjustment for B. Such a simple indirect comparison is unlikely to be reliable (see Song et al 2000)

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Appendix C Survey results, practice point rationale and plain language summary

3C1 Surveys

3C1.1 Health professional opinion on the use of exercise for the management of ankylosing spondylitis

3C1.1.1 Introduction provided to respondents

A Consensus Statement has been developed by a group of 10 Physiotherapists and a Rheumatologist, with the overall goal of providing guidance for exercise prescription for ankylosing spondylitis (AS) in Australia.

Each of the proposed recommendations is the result of a structured process that included: identification of key topic areas (KTAs); a systematic literature review for each KTA; identification of levels and quality of available evidence for each KTA, as well as relevance to the Australian setting. This information was combined with the collective opinion of the group to derive the recommendations.

The purpose of the survey is to obtain information from a broader group of Health Professionals to inform the Strength of Recommendations. The main part of the survey comprises each draft recommendation, with questions on your support for the statement, and whether you think it will modify your practice. Feedback from people with AS is being sought in a similar way. Please note that the supporting information regarding the evidence for each recommendation will be provided in the final publication.

This anonymous survey has been approved by the Tasmanian Social Sciences Human Research Ethics Committee and your consent will be implied by its completion and submission. Thank you for your interest in this project.

3C1.1.2 Questions

For each of the ten recommendations in turn, respondents were asked:

How strongly to you support this statement?

- Responses on an 11 point rating scale, with 0 labelled ‘I do not support this statement at all’ and 10 labelled ‘I fully support this statement’

Please indicate how much this statement will modify your practice

- Responses required from one of the following:
  This statement will modify my practice significantly
  This statement will modify my practice somewhat
  This statement will not modify my practice as I am already doing this
  This statement will not change my practice as I do not want to change

This statement does not apply to my practice

- Comment (optional)

3C1.2 Survey: Patient opinion on the use of exercise for managing ankylosing spondylitis

3C1.2.1 Introduction

About this Survey: For many years, it has been known that exercise is beneficial for people with Ankylosing Spondylitis (AS). Research has shown that when people perform the right sort of exercise regularly, they are usually able to improve their pain and fatigue, and increase or maintain their movement (mobility of spine and other joints), strength and overall fitness. However, there is less evidence to guide health professionals and patients regarding different aspects of exercise 'prescription', such as, what sort of exercises are best, how often and many should be performed? To help address this problem, a Consensus Statement has been developed by a group of Australian Physiotherapists and a Rheumatologist who are very experienced in managing AS. It consists of ten recommendations, with brief dot points to provide a little more detail on each. All the recommendations are based on a combination of the available research, and the 'consensus' opinion of the group. The overall aim is to help guide exercise prescription, and ensure that people with AS get the best results for the time they invest in their AS exercises.

This anonymous survey consists of some questions regarding your own experience with AS, followed by a question asking how you rate the importance of each recommendation. There is the opportunity to add comments, which may be added to a web link in the future, in order to benefit others with this condition. Your consent regarding this survey will be implied by its completion and submission. Please note that the researchers are not able to gain access to your personal details, and if you choose not to complete the survey no information will be retained. This study has been approved by the Tasmanian Social Sciences Human Research Ethics Committee.

3C1.2.2 Questions

For each of the ten recommendations in turn, respondents were asked:

How important is this statement to you?

- Responses on an 11 point rating scale, with 0 labelled ‘Not important to me at all’ and 10 labelled ‘Highly important to me’

Table 3C1 Patient (n=78) and Health Professional (n=32) Survey Results

Recommendation	Patient Rating - Importance	Health Professional (HP) Rating - Support	Recommendation will modify practice (HP, %)	Recommendation is already my practice (HP, %)	I do not want to modify my practice (HP, %)	Does not apply to my practice (HP, %)
1. Assessment	8.3	7.2	35	35	0	29
2. Monitoring	8.2	8.1	42	42	0	14
3. Safety	8.4	8.6	17	75	0	8
4. Disease management	8.0	7.3	17	50	8	25
5. AS-specific exercise (mobility)	8.7	9.4	17	67	0	17
6. AS-specific exercise (other)	8.9	9.3	8	75	0	17
7. Physical activity levels	8.9	8.9	17	67	0	17
8. Dosage	8.6	9.0	8	75	0	17
9. Adherence	8.4	9.58	25	58	0	17
10. Setting	8.48	9.25	25	58	0	17
Mean for all recommendations	8.46	8.66	21.1	60.2	0.8	17.8

Table 3C2 Rationale for Practice Points

Topic	Practise Point	Rationale
C2.1 Assessment	The Bath Ankylosing Spondylitis Metrology Index (BASMI) is the most widely reported, validated objective axial mobility measure	The Bath Ankylosing Spondylitis Metrology Index (BASMI) [1], developed in 1994, remains the most widely reported composite measure [2-8] and was considered by the group to be a clinically useful measure in exercise prescription. It has been found to have good validity and reliability [1, 9, 10].
	BASMI is associated with quality of life, physical function and psychological status	A number of (largely non-controlled) cross-sectional studies have found relationships between axial mobility (anthropometric) measures and self-reported domains such as physical function, disability, quality of life, psychological status and disease activity [3, 4, 7, 8, 11-17].
	The BASMI 10-point scoring scale (tabular or linear) is recommended over the 3-point scale	The two 10-point scoring methods (tabular or linear) have been found to have improved sensitivity to change over the original 3-point scoring scale [18], and are therefore more clinically useful for evaluation of exercise effectiveness.
	Imaging review/ discussion with medical team may be indicated for more advanced disease	As per safety section, knowledge about the location and extent of any ankylosis is pertinent to safe exercise prescription
	Tape-based hip internal rotation measure is a responsive measure for hip involvement	Maksymowych et al [10] have developed an alternative composite AS mobility measure, the Edmonton AS Metrology Index (EDASMI), which has comparable construct reliability and greater sensitivity to change over BASMI. The relatively large EDASMI trial also supported the measurement of chest expansion at xiphisternal level, hip internal rotation and lumbar lateral flexion as measures responsive to change.
	Strength, balance or cardio-respiratory function should be assessed as required	Simple measures to assess these areas can inform exercise strategies and goals appropriately

C2.2 Monitoring	Feedback, particularly mobility measures, can be important for exercise adherence.	In clinical practice, patients appear to value the objective information provided by assessment and it appears to have a positive effect on exercise behaviour [19]. Van Weely [16] found that self-reported function was typically reported as being more impaired than measured function. Therefore, objective measures appear to provide as additional perspective to other scores which rely on self-report. When health professional access is not possible or appropriate, self-monitoring techniques for axial mobility may be useful.
	BASMI raw scores are more sensitive to change than index scores	May be useful for patient feedback [20]
	In BASMI, lumbar side flexion is the most sensitive to change	As above
	The Edmonton AS Metrology Index (EDASMI) may be useful for patient self-monitoring	As it is tape measure based and comprises only 4 measurements, it may be suitable as a patient self-monitoring tool [10, 20].

C2.3 Safety	Most types of exercise are safe for the majority of patients. However, the following require assessment on a case by case basis, and may be contra-indicated in more advanced AS: High impact exercise/ physical activity (e.g. contact sports, martial arts, four wheel driving, boating in rough seas, fairground rides) High velocity or strongly resisted exercise, especially trunk flexion/ rotation	It is widely accepted that there is paradoxical spinal osteoporosis in AS [21], which appears related to disease activity and duration, and has an incidence of 18-67% [22]. As may be expected, decreased shock absorption can be a property of an ankylosed spine [23]. Associated with the combination of spinal osteoporosis and ankylosis [24], is an increased spinal fracture risk in AS of between 14 and 19% [25, 26], which is more likely to result in spinal cord injury (SCI) than in a non-ankylosed spine [27-30]. Evidence based guidelines for physical activity for people with arthritis, osteoporosis and low back pain state that those with stable arthritis, osteoporosis or low back pain (without ongoing joint damage) can safely perform aerobic or resistance exercise (evidence Level 2, Grade A/B). However, it is recommended that people with significant osteoporosis avoid heavy weight bearing, especially trunk flexion (Level 2, grade A evidence) and rotation (Level 2, grade C evidence) [31]. Some information on appropriate activities is provided in the UK National Ankylosing Spondylitis Society's exercise publication 'Back to Action' [32]. Five controlled cross-sectional observational studies were found which assessed aspects of balance in AS. The literature appeared to confirm the WG's clinical observations, that early/ mild AS does not appear to impact on spinal position sense [33] or balance tested on a platform with a low level of perturbance [34]. However, for advanced disease, postural control in standing, bilateral stance postural stability and balance during gait were all diminished in AS compared with controls [35-37]. A number of reviewers have investigated the association of cardio-vascular morbidity with AS [38-48], with consistent findings of small increases in cardio-vascular risk factors, such as athero-sclerosis, hypertension and ischaemic heart disease, in association with advanced disease severity. There was a statistically significant association of cardio-vascular risk factors with decreased spinal mobility (BASMI) [38, 40]. The risk ratio for myocardial infarction after meta-analysis of 3279 patients with AS was 1.38 [49].

	Exercise which excessively challenges balance, postural stability or cardio-pulmonary function (in a non-controlled environment)	13 studies were found investigating various aspects of pulmonary function in AS, including 7 controlled cross-sectional cohorts. Although there was one conflicting study which found no decrease in exercise tolerance in AS [50], the others all found a degree of reduction in pulmonary function. In general, reduced pulmonary fitness was inversely associated with BASMI score [47, 51] and chest expansion [51-55]. Peripheral strength [56], maximal inspiratory pressure [57] and diaphragm excursion [58] were also associated with exercise capacity.
	Excessive spinal or peripheral joint mobility gain where there is adjacent ankylosis	One small study investigated changes in sagittal spinal balance in advanced AS, finding an association with pseudarthrosis, which was most prevalent at T11/12 level [59] and there is an association of atlanto-axial subluxation with radiographic change and disease duration [60]. There was anecdotal evidence of pain/ discitis following extension exercises in a person with partial spinal ankylosis
	Excessive end range mobility gain following total hip replacement	A longitudinal study of 95 total hip arthroplasties identified anterior dislocation as a potential complication in patients with advanced spinal changes [61].

C2.4 Disease management	Exercise could theoretically be a mediator of inflammation in AS, but trial results have been conflicting	As per paper
	Stabilisation with biological therapy can be a 'window of opportunity' to optimise mobility and physical fitness.	Two studies [62, 63] found improved compliance with exercise once patients were stabilised on anti-TNF, supporting the WG's view that commencement of a biological medication may be a 'window of opportunity' to optimise mobility, strength and physical fitness for individuals with AS. However, other studies suggest there is a risk of weight gain, in association with decreased physical activity, once stabilisation with biological therapy is attained [64].
C2.5 AS-specific exercise (mobility)	Mobility goals may vary from restoration of full spinal range and normal posture (in early, well controlled disease), to maintenance of existing range (in later disease).	Clinical experience of WG. Not reflected in studies, as different groups (early vs late AS) have not been studied.
	Exercise choice (e.g. specific proprioceptive neuromuscular facilitation techniques) can be tailored to target movement or functional deficits	In the 1880s, Bulstrode et al [65] developed a series of proprioceptive neuromuscular facilitation (PNF) stretches specifically designed to be performed by individuals with AS, without the need for a partner. These 'contract relax' stretches remain in widespread use, and in the experience of the WG appear effective. A randomised trial showed superior results compared to static stretching for hip joint range, but this has not been repeated for other regions, although Kraag [66] mentions (without describing) PNF techniques.
C2.6 AS-specific exercise (other)	There is preliminary evidence for modified Pilates, tai chi, incentive spirometry and global postural re-education (GPR) as effective modalities	Single small RCTs (with group sizes of 11-30) have demonstrated effectiveness for these exercise types – as detailed in Appendix B, section 1.4.
C2.7 Physical activity	No one activity has been found to be superior.	Falkenbach surveyed 1538 people and did not find one sport more beneficial than another [67].

	Regular interruption of sedentary activities should also be encouraged	Reduction of sedentary behaviour (independently of PALs) is also gaining increasing attention in the literature, [68], including the relationship between being sedentary and physically active in all aspects of living. Guidelines have consequently incorporated the importance of reducing / interrupting sitting time as regularly as possible, [69, 70]: anecdotally this is also a beneficial strategy for managing AS related stiffness.
	Occupational, transport and leisure activities also contribute to total physical activity levels	These exercise types are beyond the scope of this review- however, can obviously contribute to total physical activity levels. A short-term (six week) study of swimming and a home exercise program (HEP), walking and HEP or HEP alone, resulted in a statistically significant improvement in mobility (BASMI), quality of life (QoL) and pulmonary function (vital capacity) measures, with additional gains in maximal oxygen consumption (pVO2) and six minute walk test for the walkers and swimmers [71].
C2.8 Dosage	Factors which may indicate modification of baseline exercise dose include: pain/ fatigue; disease activity and any secondary AS consequences (cardio-respiratory, ankylosis, osteoporosis, balance impairment)	Since up to 30% of individuals with AS meet the criteria for fibromyalgia [72], and those with persistent pain have been shown to have a hyperalgesic response to moderate to high intensity exercise [73], there may be reasons why it may make clinical sense to commence with a lower absolute dosage than otherwise recommended. In other words, the baseline and progression dosage relative to the individual concerned is important [74], noting that a low *absolute* baseline dose should not preclude progression to a physiologically adequate one over time [75].
	Dosage progression (titration) should balance individual exercise response with training for physiological change	No evidence was found for adverse events or 'over-dosing' of exercise in AS. However, overtraining is a well-recognised phenomenon in the PAL literature, with excessive exercise hypothesised to produce an increase in systemic inflammation [76]. In addition, a more rapid rate of change of dosage, as well as the total amount, have been shown to be determinants of injury [70]. At least as important is the concept that an 'over-dose' may lead to a poor exercise experience and thus activity avoidance [77], therefore careful titration is recommended.
	Mobility exercise can be incorporated in regular breaks from sitting	Whilst more epidemiological studies are required, there is sufficient evidence for national guidelines to recommend frequent interruption of prolonged sitting [70]. There is no indication that a set of stretch or mobility exercises have to be done consecutively, so if performed as a break from prolonged sitting may have a dual purpose.
	Short-term more intensive	The reported dosages of higher quality papers may be useful in guiding an intensive program, for

	doses may be appropriate for specific purposes.	example, in order to attain optimal spinal mobility following diagnosis.
C2.9 Adherence	Group settings and monitoring have been shown to support adherence in AS	In the early 1990s, Barlow studied the effects of self-help AS groups in a cross-sectional study, [78, 79], finding that group members had a higher belief in the effectiveness of exercise and were more likely to perform it regularly. A qualitative study by Porter [19] found that patients valued anthropomorphic measurements in supporting exercise behaviour.
C2.10 Setting	AS-specific group therapy and warm water exercise (hydrotherapy) may be beneficial adjuncts to an individual's regular home exercise program.	The 2008 Cochrane review found that there was evidence to support 'group physiotherapy' over home exercises, and 'combined inpatient spa-exercise therapy followed by group physiotherapy' over group physiotherapy alone [81]. Two recent studies have compared out-patient group rehabilitation [82] and group Pilates [83] to no active intervention. These higher quality RCTs (rated 7/10 and 8/10 on the PEDro scale) both demonstrated significant improvements in mobility (BASMI and chest expansion) and disease activity (BASDAI). The WG acknowledges the lack of good quality trials involving warm water exercise in a non-residential setting. However, clinical experience and trials of balneotherapy (which usually incorporate an active exercise component) suggest that it can be effective, especially in more advanced disease. NB. No trials investigating the same exercises in cooler water (i.e. less than 30°C) were found. However, the thermal properties of water as an exercise medium are considered important, and anecdotally, mobility exercise appears more effective and comfortable in warmer water.
	Where available, exercise supervision appears to enhance effectiveness	Although home-based exercise has been shown to be effective[84], a component of supervision appears to offer the greatest benefits [85, 86]. NB This PP was added following the final literature review.

Figure 3C1 Plain Language Recommendations and Practice Points

Exercise for Ankylosing Spondylitis (AS): A Consensus Statement
Plain Language Summary
For people who have AS at any stage, including early stages

Recommendation 1: Assessment for Exercise
People who have AS should have a thorough assessment which can be repeated at regular intervals. It should include all aspects that may relate to planning of exercise, such as personal circumstances, history of condition and measures of how AS has affected movement

- The assessment helps to inform the best exercise combination for each person, that is, where to start

Recommendation 2 : Monitoring
A regular review should be offered, so that people with AS can feel confident that they are getting the most benefit from their exercises. This should happen at least once per year and more often where required

- Feedback (such as mobility measures) can be helpful for motivation to continue exercise
- Self-monitoring techniques may be useful where health professional access is not possible

Recommendation 3: Safety
Any physical effects of the condition must be considered, especially for those with more severe or later disease. This includes any spinal fusion, balance or mobility change, osteoporosis (bone thinning) or general fitness effects of the condition

- *Most types of exercise are safe for the majority of people with AS.*
- However, exercise or activities that are 'high impact' or strenuous should be assessed on a case by case basis
- Examples of activities to avoid if you have significant spinal fusion (ankylosis):
  - contact sports
  - martial arts
  - four wheel driving
  - boating in rough seas
  - fairground rides
  - forced movements to increase mobility (including after hip replacement)
- People who have osteoporosis (bone thinning) should avoid strenuous or repetitive trunk bending and twisting
- Some activities may need adaptation to manage any balance or fitness (breathing) restrictions
- *These precautions to do not apply to people who have well-managed and early or less severe AS*

Recommendation 4: Condition Management
When people with AS are treated with 'anti-TNF' medication, they should continue with regular exercises, as the combination is more beneficial than the medication on its own

Starting on a biological medication may provide a 'window of opportunity' to obtain the best possible movement, strength and fitness

- Exercise has been shown to decrease inflammation, but the exact effects in AS are not yet clear

Recommendation 5: Exercise to treat AS (mobility)
The most important exercises are those that help keep the spine (and other affected joints) moving. Mobility measures may help guide which exercises should be chosen for most benefit

Recommendation 6: Exercise to treat AS (other)
Stretching, strengthening, and heart/ lung ('cardio') fitness are also important for a balanced exercise program.

- People with early AS may be able to keep or restore full movement
- Others who have had AS for longer may be aiming to keep their existing movement
- There are small studies to show that hydrotherapy, spa exercise, Tai chi, swimming, Pilates and walking have benefits in AS

Recommendation 7: Physical activity for general health
Regular physical activity is important for general health, well-being and the best possible level of function.

- The research does not show that one activity is better than another
- Avoiding sitting for too long (more than half an hour) is recommended
- Lifestyle physical activity (for work, transport or leisure) may also help with managing AS symptoms

Recommendation 8: Dosage
Advice about how much, how often and how vigorously exercises should be performed should be tailored to a person's needs, lifestyle, and condition.
(a) For mobility, stretch & postural exercise, consistency is important
(b) For other types of exercise, national physical activity guidelines are helpful, but may require adjusting due to AS.

- When starting to exercise, factors such as pain, fatigue and any consequences of AS should be considered
- The ideal amount of exercise for each person will take into account these factors, but still be enough to have an effect
- Changes to exercise dosage should be matched to a person's goals and response to exercise
- Mobility exercises can be 'tagged' to other activities, such as a break from sitting down at work
- More intensive exercise, for a limited time, may be helpful for a particular goal

Recommendation 9: Adherence
It is important to consider motivation for continuation of regular exercise and ongoing self-management.

- The challenges of keeping going with a regular exercise routine are acknowledged and should be supported
- Group exercise sessions and monitoring (of spinal measures) have been shown to be helpful for ongoing motivation

Recommendation 10: Exercise Setting
In all exercise choices, a person's preferences are important, in order to increase the likelihood of exercises being carried our regularly and on an ongoing basis.

- Hydrotherapy and exercise groups may provide extra benefit in addition to individual exercises
- Where available, exercise supervision appears to enhance effectiveness

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3.11 Postscript: Evidence published following completion of this study

The published paper systematically reviewed the literature published up until 1st July, 2015. This limitation was addressed by repeating the search strategy utilised in the study from that date until 25th August 2018, revealed six additional RCTs that met the inclusion criteria, and these are summarised in Table 3.1. Two RCTs [2, 3] aimed to increase balance parameters in people with axSpA, both finding that there were significant between group differences in a range of balance parameters, favouring the intervention group. A slightly larger RCT (35 participants per group), compared the effects of a walking and stretch program, with a group performing stretching exercises alone [4]. Significant improvements in cardio-pulmonary capacity were measured in the walking group, despite the fact that the exercise program described did not meet the ACSM guidelines for physiological effectiveness (Table 1.1). Taken together, these interventional studies provide limited additional support for the concept presented in this chapter of an individually tailored exercise program that addresses measured and potential deficits in mobility, strength, cardio-pulmonary and functional parameters, including balance.

Further supporting evidence for also retaining mobility exercise as a key recommendation is provided by the cross-sectional observational study by O'Dwyer et al, who found significant reductions in validated measures for mobility, strength and cardio-respiratory function in 39 adults with AS, compared to controls sourced from the general population by advertising, who were matched for gender and age. There was also a strong positive correlation between spinal mobility and physical function [5], thus recommendation 5 is strengthened.

A further RCT found that a behavioural intervention aiming to increase physical activity was also successful in increasing spinal mobility – although the effect of additional mobility exercises was not tested [6]. This latter study, however, strengthens recommendation nine of the CS regarding the prioritisation of adherence in the development of exercise programs.

Lastly, a pilot study investigated the use of a computer-based 'virtual avatar' exercise program [7] – however, since insufficient detail was provided on the exercise program and outcome measures (Table 1.1), it is not possible to incorporate such strategies into evidence based guidance at this time.

Table 3.6 Studies published since the publication of the AS consensus statement

Author (year)	Study Type	Groups (n)	Main outcome measures	Main findings
Demontis (2016) [2]	Quasi-randomised, single-blinded study	Rehabilitation (supervised) + education (22) Education alone (20)	Balance parameters measured by stabilometry, BASMI, BASFI, BASDAI	Significant improvement in sway density; trend towards improvement in other parameters.
Gunay (2018) [3]	RCT	Balance exercises + spa based rehab (11) Spa based rehab only (10)	Balance parameters, BASFI, BASMI, BASDAI, AsQoL	Improvement in balance measures for balance intervention group; improvement in other parameters for both groups
Jennings (2015) [4]	RCT	Walking + stretch exercise (35) Stretch alone (35)	Cardio-pulmonary capacity, 6MWT, BASFI, BASMI, BASDAI, AsQoL	Improvement in cardio-pulmonary capacity & 6MWT; similar improvement in other measures in both groups
Karahan (2016) [7]	RCT	'Exergames' (30) No exercise (30)	Pain NRS, BASFI, BASDAI, AsQoL	Improvement in pain, BASFI, BASDAI & ASQoL scores in the intervention group
O'Dwyer (2016) [5]	Cross-sectional, controlled, observational study	Adults with AS (39) Matched controls (39)	Validated measures of mobility, strength, cardio-resp. function, body composition	Significant decrease in mobility, strength, cardio-respiratory function, & increase in body fat, in AS group
O'Dwyer (2017) [6]	RCT	PA behaviour change intervention (20) Usual care (20)	Accelerometer measured PA, validated measures of mobility, strength, cardio-resp. function, body composition, ASQoL, BASFI, BASDAI	Significant, mod-large increase in PA, improved BASMI & ASQoL in intervention group. No significant change in strength, cardio-resp. function, body composition, BASFI or BASDAI.

Exergames – movements in co-ordination with a 'virtual avatar' computer program; callisthenics - gross motor/ body weight exercises; BASFI Bath AS Functional Index; BASDAI Bath AS Disease Activity Index; ASQoL AS Quality of Life score; BASMI Bath AS Metrology Index; BASFI Bath AS Functional Index; 6MWT six minute walk test; PA = physical activity

3.12 References - postscript

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Chapter 4: Methods

4.1 Preface

The second phase of this thesis aims to strengthen the evidence for exercise in axSpA, by obtaining further information about the lumbar paraspinal muscles, which may inform the future development of specific exercise management strategies. The participants were a sub-group of the Tasmanian Ankylosing Spondylitis Study (TASS). This chapter describes TASS and the additional research methods used within the sub-study.

4.2 The Tasmanian Ankylosing Spondylitis Study (TASS)

This population based, longitudinal inception cohort study aimed to investigate the relationship between inflammation and demonstrated structural damage in early axSpA. The study was approved by the Health and Human Research Ethics Committee (Tasmania) - Network approval number H0009856. The study population were Tasmanian adults with rheumatologist-diagnosed inflammatory back pain (IBP), and / or other extra-articular features consistent with spondyloarthritis, according to the European Spondylarthropathy Study Group (ESSG) criteria for spondyloarthritis. The criteria are ‘inflammatory spinal pain’ or ‘synovitis’ (asymmetric or predominately in the lower limbs), and one or more of the following variables [1]:

- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Urethritis, cervicitis or acute diarrhea within one month before the onset of arthritis
- Buttock pain alternating between right and left gluteal areas
- Enthesopathy
- Sacroiliitis

Inflammatory back pain is further defined by ESSG as: “History or present symptoms of spinal pain in back, dorsal, or cervical region, with at least four of the following: (a) onset before age 45, (b) insidious onset, (c) improved by exercise, (d) associated with morning stiffness, (e) at least 3 months duration” [2].

Participation in the sub-study was offered to those consecutively referred to TASS by rheumatologists and other health professionals. Exclusion criteria for the sub-study were: previous spinal or pelvic surgery; any known contra-indications to MRI, such as metal

implants, pacemakers or claustrophobia; significant co-morbidities which may influence mobility, and, previous instruction in lumbar muscle strengthening exercises. However, in this instance no exclusion criteria were identified amongst potential participants prior to the study. Written informed consent was gained for both participation in the study and to undergo the MRI procedure.

4.3 Measures utilised for the sub-study

C-Reactive protein (CRP) is non-specific acute phase reactant of hepatic origin, which is commonly used to monitor inflammation in rheumatologic diseases [2]. It is measured in milligrams per litre, and values were obtained from medical records for the date closest to the MRI scan.

Sacro-iliac radiographic grade (0-4)

Sacroiliitis was assessed by a standard antero-posterior radiograph (x-ray) of the pelvis, and the degree of sacro-iliac (SI) joint change graded by a physician according to the ASAS recommended criteria [4] (Table 4.1):

Table 4.1: Sacro-iliac radiographic grades for AS (modified New York criteria)

Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimal abnormality – small localized areas with erosion or sclerosis, without alteration in joint width
Grade 3	Unequivocal abnormality – moderate or advanced sacroiliitis with one or more of: erosions, sclerosis, widening, narrowing or partial ankylosis
Grade 4	Severe abnormality – total ankylosis

Magnetic Resonance Imaging (MRI) scans

An ultimate goal in exercise therapy is improved function, yet the part that muscles play in overall physical function is complex to understand and measure, and this is particularly so with regard to the lumbar spine and pelvis. However, it is widely recognised that, without

muscle control, the lumbo-pelvic region lacks stability [11] and thus a dynamic platform for most bodily movement. A further complexity is the contribution of central nervous system (CNS) motor control, for which pain is a known major modifier [12]. Static images, taken in a supine position, cannot therefore represent all aspects of muscle 'fitness for purpose', however, they have been shown to be useful surrogate markers in relation to function, as follows:

(a) Morphology and function

Muscle size and mass have been found to peak at age 24, and decrease by approximately one per cent annually from the fifth decade [13]. Accelerated loss of muscle mass is termed sarcopaenia: 'primary' is said to be age related, and 'secondary' is when there is association with immobility, inactivity or disease [14]. Although total muscle mass and function do not always predict each other [15-16], in the lumbar spine a recent study found significant correlations between multifidus/ composite trunk muscle size and functional tasks such as 'timed up and go' and balance tests [17]. And a longitudinal MRI study of 962 participants demonstrated an inverse relationship between paraspinal muscle CSA and levels of disability, after adjusting for confounders [18].

(b) Muscle quality and function

One explanation for the lack of direct association between total muscle mass and function is that muscle quality can change over time. Muscle architecture (fibre type and length) may degenerate [19], in association with fatty infiltration, that is, deposition of adipocytes within a muscle's fascia. This is known as inter-muscular adipose tissue (IMAT) [20] and is essentially ectopic fat deposition. There is now substantial evidence that IMAT is a significant predictor of muscle function and overall mobility and physical function [21], as well as metabolic dysfunction, due to decreased glucose tolerance [22], and as such is a predictor for mortality from mid-life onwards [23]. There is limited evidence from observational studies that paraspinal IMAT is associated with a loss of functional capacity [24-25].

(c) Paraspinal muscle symmetry and function

Several studies have found an inverse association between paraspinal (particularly LM) CSA and unilateral low back pain – whether the latter is 'non-specific' or associated with disc findings [26-28] or with unilateral bony structural change such as scoliosis [29] or stenosis [30]. However, the importance of these findings remains controversial [31]. No studies were

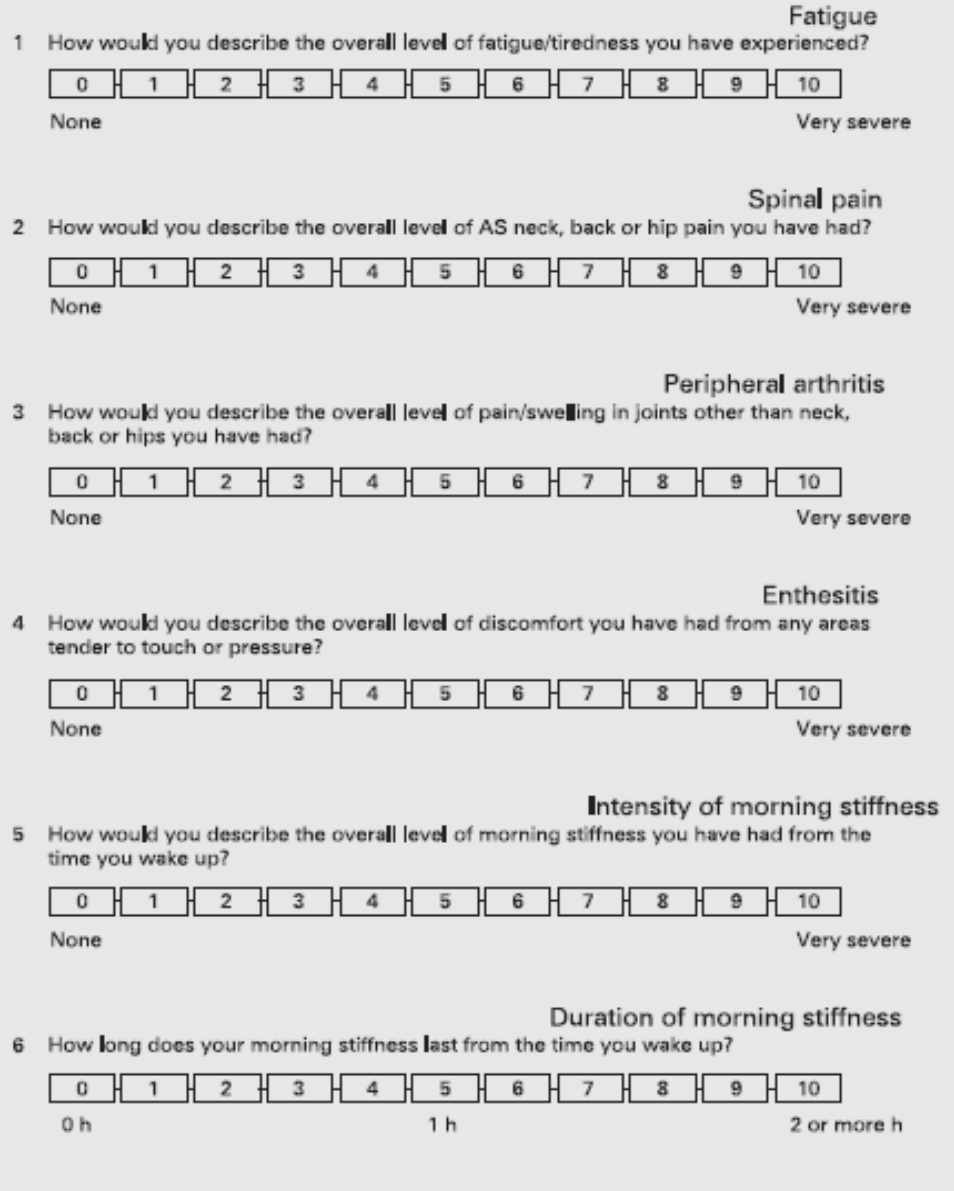
found which directly examined the relationship between paraspinal muscle symmetry and function.

In summary, assessment of muscles and their function is complex, particularly in the lumbar spine. Each MRI measure acts as a partial descriptor only, hence the selection of three different measures (size, represented by CSA, IMAT and symmetry) to provide more detailed information. To further enrich the information, each measure was performed at lumbar spine levels L2/3 to L5/S1. Since the lower fibres of LM have attachments to the sacro-iliac joint capsule via the thoraco-lumbar fascia [32], comparison of levels could provide useful information about the disease, and potentially influence exercise selection.

Bath Ankylosing Spondylitis Activity Index (BASDAI).

Since up to 40% of patients with definite AS do not have elevated inflammatory markers, a patient reported index is commonly used in conjunction with objective inflammatory marker monitoring [3]. The BASDAI questionnaire comprises six questions and the numerical rating scale (NRS) version was used during the TASS study (figure 4.2).

Figure 4.1 NRS version of BASDAI patient reported outcome measure [2].



Total score = (Q1 + Q2 + Q3 + Q4 + (Q5 + Q6 / 2)) / 5 where Q1= score for question 1, Q2= score for question 2 and so on.

Back pain in previous week – NRS (0-10) As recommended in the ASAS core assessment set, a 0-10 numerical rating scale was used to assess back pain during the previous week [5].

Ankylosing Spondylitis Quality of Life (AS-QoL) The AS-QoL comprises 18 questions in the following domains: physical mobility; energy; pain; emotional reactions and sleep. It has shown excellent internal consistency (α=0.89–0.91) and test-retest reliability (rs=0.92). Construct validity was tested by examining the ASQoL domains in comparison

with previously validated measures - the Nottingham Health Profile (NHP) and Bath AS Functional Index (BASFI). Spearman rank correlation coefficients for these comparator measures were as follows: physical mobility 0.78; energy 0.74; pain 0.81; emotional reactions 0.72; sleep 0.54; social isolation 0.53, and BASFI 0.72 [6].

Bath AS Metrology Index

The most commonly used instrument for measuring axial mobility is the Bath AS Metrology Index (BASMI) [7], which consists of five objective measures, as shown in Table 4.2:

Measure	Method	Unit
Spinal posture	Tragus to wall distance: distance from ear to wall when standing upright with back to wall	cm
Lumbar spine mobility - flexion	Schobers test: distraction of two points drawn 15cm apart on the lumbar spine (using the posterior superior iliac spines as bony landmarks), after moving from an upright to a flexed position	cm
Cervical spine mobility - rotation	Head turning measured in supine with a goniometer – mean of left and right	degrees
Hip mobility - abduction	Distance between ankles on bilateral hip abduction whilst supine	cm
Lumbar spine mobility – lateral flexion	Distance travelled by fingertips towards floor, when performing lateral flexion from an upright position – mean of left and right	cm

There are a two scoring systems: the ten point scale was chosen for our study due to its superior validity [8] and each item is scored as in Table 4.3. The mean score of the five measures represents the total BASMI score.

Table 4.3 Bath AS Metrology Index 10 point scale

Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Tragus to wall (cm)	≤ 10	10-12.9	13-15.9	16-18.9	19-21.9	22-24.9	25-27.9	28-30.9	31-33.9	34-36.9	≥ 37
Modified Schober's (cm)	≥ 7.0	6.4-7.0	5.7-6.3	5.0-5.6	4.3-4.9	3.6-4.2	2.9-3.5	2.2-2.8	1.5-2.1	0.8-1.4	≤ 0.7
Inter-malleolar distance (cm)	≥ 120	110-119.9	100-109.9	90-99.9	80-89.9	70-79.9	60-69.9	50-59.9	40-49.9	30-30.9	≤ 20
Cervical rotation (degrees)	≥ 85	76.6-85	68.1-76.5	59.6-68	51.1-59.5	42.6-51	34.1-42.5	25.6-34	17.1-25.5	8.6-17	≤ 8.5
Lumbar side flex (cm)	≥ 20	18-20	15.9-17.9	13.8-15.8	11.7-13.7	9.6-11.6	7.5-9.5	5.4-7.4	3.3-5.3	1.2-3.2	≤ 1.2

The actual values for two components of BASMI (Schober's test and lumbar lateral flexion) are additionally reported in our study, since they are specific to the region of interest and provide a visual indication of spinal stiffness.

Baecke Habitual Activity score This questionnaire has domains for physical activity in work, sport and leisure, each having a maximum score of five points, for a total score of 15 [9]. It was found to have good repeatability, and moderate validity (similar to an exercise diary) [10].

Chapter 5 includes details regarding the MRI imaging and analysis and statistical analysis (section 5.4).

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Chapter 5: Size, symmetry and quality of the lumbar paraspinal muscles in axial spondyloarthritis: a pilot study

5.1 Preface

The previous chapters identified that there is minimal evidence to support the development of exercise recommendations for axSpA that address the details of muscle fitness, such as strength, endurance, power or motor control. In contrast, strengthening (resistance) exercises are an integral component of well-established exercise guidelines for the maintenance of health [1, 2]. In axSpA, there is limited and somewhat conflicting, evidence that muscles may be primarily or secondarily affected by the condition [3-6], and a recent hypothesis that biomechanical stress may play a role in pathogenesis [7-10]. The latter has led to some questions about the role of exercise in axSpA management [11, 12]. Although axSpA is a systemic disease, the initial inflammatory changes occur in the lumbo-pelvic region, and therefore the lumbar paraspinal muscles are a likely target for any primary or secondary pathological change. This exploratory pilot study therefore aimed to examine whether further investigation of muscle size, symmetry or quality is warranted, as this could be important in designing future exercise-based studies that aim to evaluate the effect of addressing any identified deficits.

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5.2 Abstract

Objective

There is little information available to inform the prescription of therapeutic strengthening exercises in people with axial spondyloarthritis (axSpA), including whether exercise should involve the 'whole body', or target specific muscles. Since axSpA initially affects the lumbo-pelvic region, information about muscles with lumbo-pelvic bony attachments could be helpful. This pilot study therefore aimed to describe and quantify the lumbar paraspinal muscles in people with axSpA.

Methods

Magnetic resonance imaging (MRI) of the lumbar spine was undertaken on 23 individuals with axSpA. Bilateral measures of total and fat cross-sectional areas (CSAs) were performed for the lumbar multifidus (MF) and lumbar erector spinae (LES) muscles separately at each vertebral level from L2/3 to L5/S1, and functional CSAs and percentages of intermuscular adipose tissue (IMAT) were calculated.

Results

IMAT was typically found in a symmetrical pattern adjacent to the muscle/ bone interfaces in both muscles. The highest percentage of IMAT occurred at the L5/S1 vertebral level. IMAT was higher in females than males, and the presence of IMAT levels >10% was distributed across the age range. There was a small association between age and IMAT (LM β 0.51, 95% CI 0.06, 0.96, LES β 0.63, 95% CI 0.06, 1.20) but none between BMI and IMAT.

Conclusion

People with axSpA have high levels of intermuscular adipose tissue in both the LM and LES muscles, which is largely symmetrical and most pronounced at the lower lumbar levels. A number of potentially complex relationships between the muscle changes, and disease pathogenesis and progression are plausible. Regardless, these data support the need to develop and test potential exercise interventions targeting these muscles in axSpA, including biomechanical effects.

5.3 Introduction

Evidence based management guidelines for axial spondyloarthritis (axSpA) consistently include exercise as a key recommendation [1, 2], supported by systematic reviews with meta-analyses that have found consistent evidence for exercise across multiple outcomes [3-6] [42] Despite such universal recommendation, there is inadequate detail regarding the parameters of exercise prescription, reflecting limitations in the evidence base. Most attention has been paid to mobility exercises. RCTs have not addressed parameters of muscle fitness (such as motor control, strength, endurance and/ or power) in people with axSpA [7].

The muscles that are typically the most symptomatic in axSpA are the lumbar paraspinal muscles. Previous MRI studies have found decreased total CSA of the paraspinal muscles in people with AS, compared with healthy controls [8], and controls with non-radiographic spondyloarthritis (nr-SpA) [9] and low back pain (LBP) [10]. Two of these studies additionally assessed muscle quality using semi-quantitative scales [8, 9]. However, there was limited information about the nature of the changes seen in individual muscles across all lumbar levels – for example, no studies were identified that examined symmetry of any spinal muscle, despite findings of paraspinal asymmetry in association with other spinal pathologies, such as scoliosis, stenosis and disc herniation [14-16]. In addition, no studies were identified that investigated IMAT and CSA at the L5/S1 level, despite it's close anatomical location to the SI joints and importance in biomechanical assessment and therapy. More detailed information about individual paraspinal muscle morphometry (size, symmetry and amount of fat within the muscle) at multiple levels, adjusted for age and sex, could therefore be helpful in designing optimally effective axSpA exercise programs. For example, it would be useful to know whether exercises designed to preferentially recruit specific muscles or spinal levels should be trialled, or whether the findings point to a more general approach. And, given that ectopic fat deposition within muscle (intermuscular adipose tissue (IMAT)) has been shown to be predictive of strength, mobility and metabolic dysfunction [11], results could inform future useful lines of enquiry which could enhance current knowledge of the axSpA disease process.

This study therefore aimed to describe and quantify the lumbar paraspinal muscles (multifidus (LM) and the lumbar erector spinae (LES) group – longissimus thoracis pars lumborum & iliocostalis lumborum pars lumborum) at multiple levels, in people with axSpA.

5.4 Methods

Study participants

This cross-sectional pilot study was a sub-study of 24 consecutive participants from the larger Tasmanian Ankylosing Spondylitis Study (TASS - Health and Human Research Ethics Committee (Tasmania) Network approval number H0009856). The latter was a prospective longitudinal inception cohort of 188 participants who met the European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthritis [12]. All sub-study participants had been diagnosed as having axSpA by a rheumatologist, and exclusion criteria were: previous spinal or pelvic surgery; any known contra-indications to MRI, such as metal implants, pacemakers or claustrophobia; significant co-morbidities which may influence mobility, and, previous instruction in lumbar muscle strengthening exercises.

TASS participants completed a series of patient reported outcome measures (PROMS) and other monitoring tests at six monthly intervals. These included: the Bath AS Disease Activity Index (BASDAI) [13]; the AS Quality of Life (AS-QoL) questionnaire [14], SI joint x-rays, and the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Those participants enrolled in the muscle sub-study additionally completed a 10 cm Numerical Rating Scale (NRS) for back pain; and the Baecke Physical Activity Score [15]. Physical parameters were obtained as follows: height in centimetres using a Leicester Stadiometer, weight in kilograms using a calibrated Heine electronic scale and axial mobility scored by completion of the Bath AS Metrology Index (BASMI) [16], using the 10 point scoring scale [17]. The latter includes two specific lumbar spine assessments: Schobers' test measures the distraction of the lumbar spinous processes on movement from an upright to a flexed position, and lumbar side flexion measures the lateral bend of the spine in a coronal plane (mean of left and right). MRIs were performed on the same day as the participant interview and physical examination. Data for symptom duration (years); C-reactive protein (CRP) and sacro-iliac x-ray grading were obtained from the TASS dataset, for the assessment point closest to the date of the MRI acquisition.

Image acquisition and analysis

Participants were positioned on the MRI patient table in a standardised crook lying position (supine lying with a pillow placed under the knees and the head and neck supported in a neutral position). MRI was performed using a 1.5 Tesla machine (Siemens AG, Germany) with true fast imaging in steady-state precession (FISP) sequence, using 14 x 7 mm contiguous slices aligned with the lower border of the body of the fourth lumbar vertebra

(L4). De-identified images were measured off-line using OsiriX medical imaging software (Geneva, Switzerland) by a physiotherapist (JM) with extensive musculoskeletal experience and additional training in measurement of paraspinal muscles on MRIs. The axial slice which most clearly identified the intervertebral disc and zygapophyseal joints at each lumbar level, from L2 to L5, was identified. For each selected slice, the LM and LES muscles on both sides were outlined along their fascial boundaries using the software's 'polygon' tool, to obtain the total cross-sectional area (TCSA, cm^2). Areas within each muscle boundary demonstrating bright signal were then outlined and measured. Based on *in vivo* correlation between the bright signal visualised within paraspinal muscles on MRI, and histological findings of adipose tissue [18], this measure was labelled fat CSA (cm^2). Functional CSA (FCSA) was calculated as (TCSA-fat CSA) and intermuscular adipose tissue (IMAT) by (fat CSA/TCSA*100) for each set of measures (muscle, level and side). Absolute and percentage differences between individual pairs of left and right TCSA and FCSA measures for each muscle and level were calculated as (largest value-smallest value) and (largest value-smallest value/largest value*100) respectively. Body mass index (BMI) was calculated as weight (kg) / (height (m))^2.

Intra-rater repeatability was tested by completion of a second set of measures for total and fat CSA for each muscle at the L2/3 and L5/S1 levels, that is, a total of 16 pairs of measures for each subject.

Statistical Analysis

Statistical analysis was performed using Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics for participant characteristics and muscle symmetry measures are presented as medians and interquartile ranges due to positive skewness for most variables. Median values for the functional, fat and total CSAs are presented graphically in bar charts stratified by sex, muscle and spinal level for right and left sides (Figure 1). Median percentage IMAT was similarly explored graphically (Figure 2). Data on muscle symmetry for total and functional CSA for each muscle was tabulated (Table 2). Differences in muscle measures at each level, after adjusting for sex, age and BMI, were estimated using linear mixed models regression, which accounts for the correlation between the repeated measures for individuals (Table 3). Separate models were fitted for total CSA, functional CSA, fat CSA and IMAT for the LM and LES muscles. Full data for CSA by muscle and sex are also reported (Supplementary Table 1).

5.5 Results

All participants completed the study, except for one who was unable to undergo an MRI scan due to previously unidentified claustrophobia. Participant characteristics stratified by sex are presented in Table 5.1. There was a broad age range of 18-68 years, and median BMI was 25.1 kg/m^2 for males and 23.4 kg/m^2 for females. For the whole group, half (11) were within 'normal' BMI range (18.5 to 24.9 kg/m^2), ten participants were 'overweight' (25 to 29.9 kg/m^2) and two were 'obese' (BMI > 30 kg/m^2). Women were younger than men (median age 28 versus 37 years) and had slightly higher BASDAI, less mobility limitation and lower reported physical activity. Median CRP was at the upper end of normal range (3.0 mg/L), indicating well-controlled disease, and a median Bath AS Metrology Index of 2.0/10 suggests most participants had mild-moderate movement limitation.

Intraclass correlation coefficients for the repeated measures using a two-way mixed-effects model were in the excellent range (Table 5.2).

Table 5.1: Participant characteristics by sex

Variable	Male, n=16	Female, n=7	Total, n=23
Age (years)	37.5 (25, 52)	28 (25, 47)	37 (25, 49)
Body Mass Index (kg/m^2)	25.1 (22.6, 26.4)	23.5 (22.3, 28.4)	25.1 (22.3, 26.8)
Symptom duration (years)	10.5 (6.5, 26.5)	8.0 (5.0, 21.0)	10.0 (6.0, 22.0)
CRP (mg/L)	3.0 (1.0, 15.0)	2.8 (1.0-5.0)	3.0 (1.0-11.0)
Sacro-iliac x-ray grade (0-4)	2.0 (1.0, 3.0)	2.5 (1.0, 3.0)	2.5 (1.0, 3.0)
Back pain in previous week – NRS (0-10)	5.7 (4.5, 6.8)	5.8 (4.5, 7.8)	5.8 (4.5, 7.8)
AS QoL scale (0-18)	5.0 (0.5, 10.0)	12.0 (6.0, 16.0)	7.0 (1.0, 12.0)
BASDAI (/10)	4.0 (1.8, 5.7)	5.3 (2.0, 5.5)	4.4 (2.0, 5.6)
BASMI (/10)	2.1 (1.1, 3.6)	1.4 (1.2, 5.2)	2.0 (1.2, 4.2)
Schobers test (cm)	5.6 (4.5, 6.0)	4.8 (3.5, 6.0)	5.5 (4.0, 6.0)
Lumbar side flexion (cm)	15.8 (12.9, 20.3)	18.7 (8.0, 19.5)	16.3 (11.0, 19.5)
Baecke Habitual PA score - work (/5)	3.06 (2.8, 3.5)	2.6 (2.4, 3.1)	3.0 (2.4, 3.3)
Baecke Habitual PA score - sport (/5)	2.5 (2.0, 3.1)	2.3 (1.8-3.0)	2.5 (2.0-3.0)
Baecke Habitual PA score-leisure (/5)	2.9 (2.3, 3.3)	2.5 (2.0, 2.8)	2.8 (2.3, 3.3)
Baecke Habitual PA score - total (/15)	8.3 (7.3, 9.4)	7.5 (6.6, 7.9)	7.9 (7.1, 8.9)

Values are presented as medians (25th, 75th percentile).CRP C-reactive protein; NRS numerical rating scale: 0=no pain and 10=most severe pain; AS QoL Ankylosing Spondylitis Quality of Life (QoL) scale: 0=best QoL, 18=worst QoL; BASDAI Bath AS Disease Activity Index: 0=lowest disease activity, 10=highest disease activity; BASMI Bath AS Metrology Index: 0=full axial range or movement, 10=highest limitation of range of movement; Schobers test: increase in distance on lumbar flexion between two marks placed 15cm apart on the lumbar spine: lower value=larger limitation to lumbar flexion; PA physical activity: higher score indicates more physical activity

Table 5.2 Intra-rater repeatability: intraclass correlation coefficients (ICC) for repeated measures using a two-way mixed-effects model

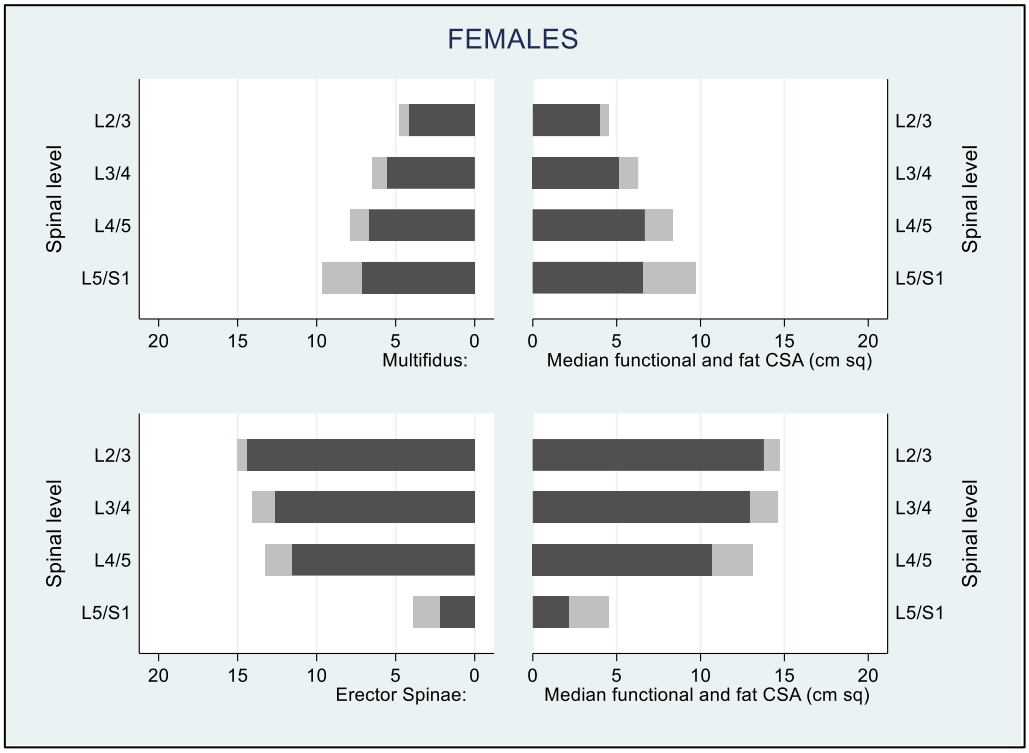
Muscle/ Level	**Total CSA ICC (95% CI)**		**Fat CSA ICC (95% CI)**	
LM	**Right**	**Left**	**Right**	**Left**
L2/3	0.862 (0.706-0.939)	0.758 (0.512-0.899)	0.985 (0.958-0.994)	0.977 (0.946 - 0.990)
L5/S1	0.913 (0.806-0.968)	0.828 (0.637-0.923)	0.931 (0.875-0.986)	0.937 (0.887-0.987)
LES				
L2/3	0.965 (0.919-0.985)	0.956 (0.900- 0.981)	0.925 (0.835-0.968)	0.992 (0.980-0.996)
L5/S1	0.770 (0.486-0.900)	0.852 (0.685-0.935)	0.926 (0.835-0.968)	0.917 (0.818-0.964)

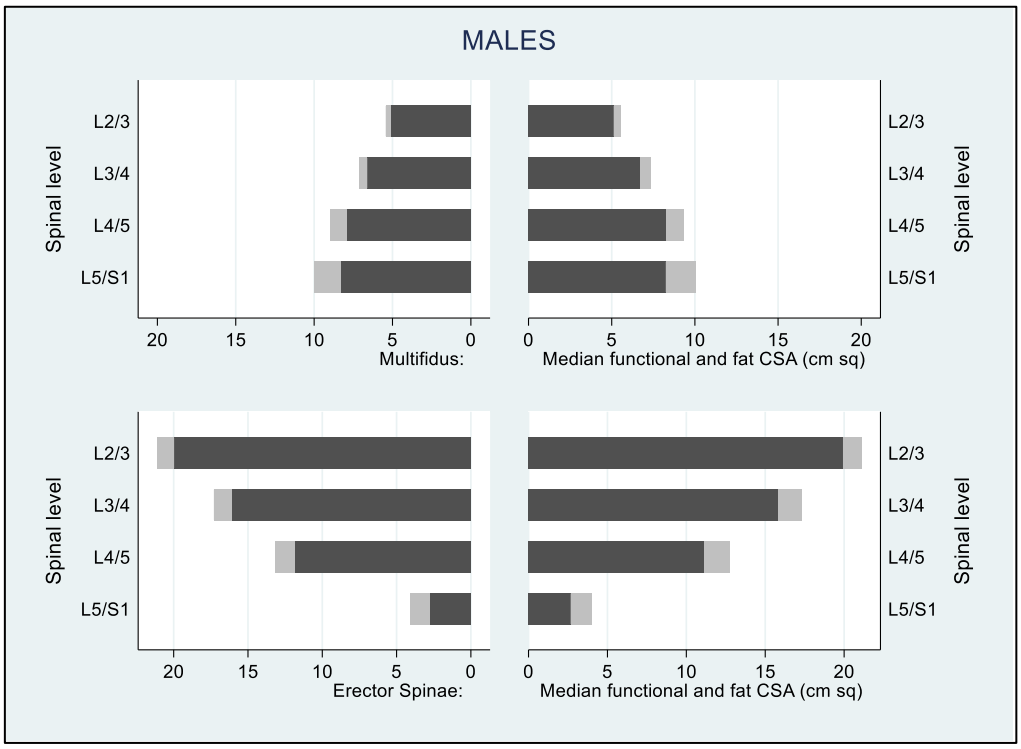
CSA = cross sectional area; LM = lumbar multifidus; LES = lumbar erector spinae

Muscle Size

Figure 5.1 illustrates the median size of muscles across vertebral levels for males and females. Total (functional + fat) CSA was higher with descending spinal levels for the LM muscle, and *vice versa* for the LES muscles. Total muscle CSAs were larger for males, and for both LM and LES, fat CSA was greater in females and increased with descending vertebral levels in both sexes.

Figure 5.1 Paraspinal fat, functional and total CSA for left and right sides in (a) females and (b) males





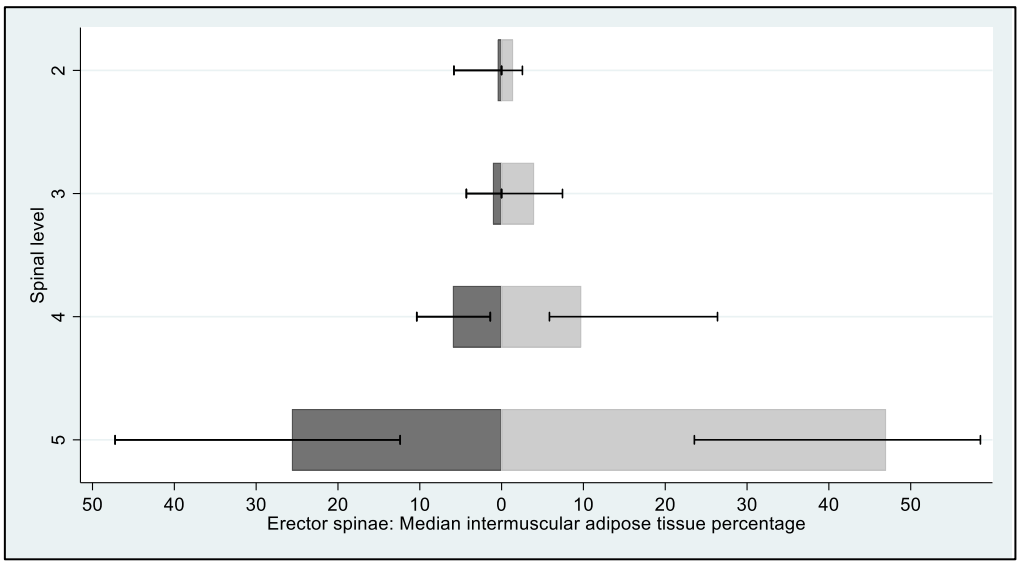
Values are Medians ■ *= functional CSA;* ■ *= fat CSA; whole bar = total CSA*

Quality

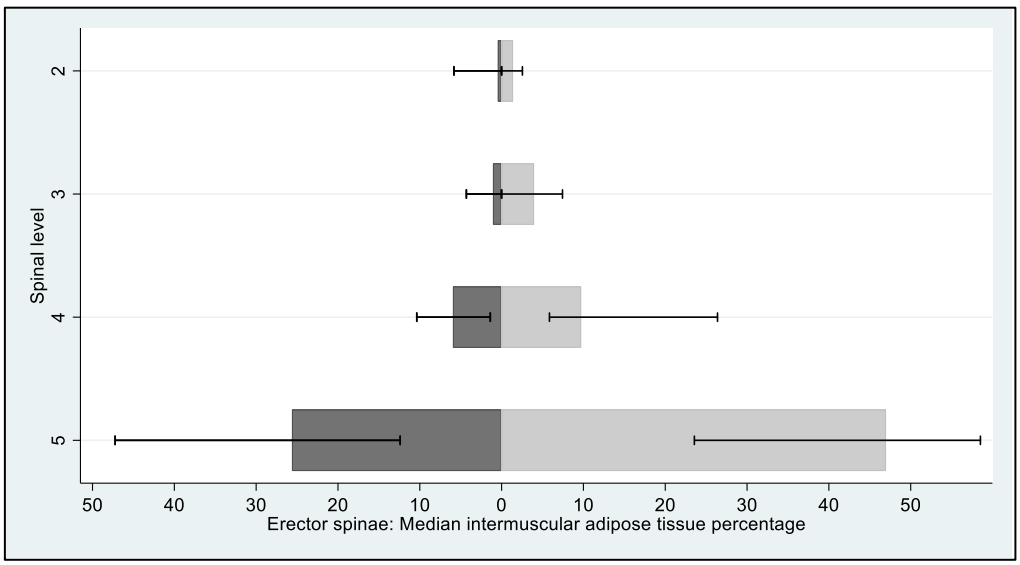
The median percentages of IMAT by muscle, level and sex are shown in Figure 5.2:

Figure 5.2 Median intermuscular adipose tissue (IMAT) percentage by level and sex for (a) LES and (b) LM

(a)



(b)



Data are medians and interquartile ranges; y axis Spinal level 2 = L2/3; 3 = L3/4; 4 = L4/5; 5 = L5/S1; ■ *= males,* □ *= females*

IMAT was commonly present, with a value of greater than 10% found in at least one level, in all but one participant. IMAT was almost exclusively located adjacent to the muscle and bony interface, that is, adjacent to the vertebral body's accessory and transverse processes for the LES, and the lamina and spinous processes for LM muscles. Thus, the IMAT formed typical shapes on the image as shown in Figure 5.3. In males, median IMAT for both muscles exceeded 10% at the L5/S1 vertebral level only. However, in females, median IMAT exceeded 10% at the L4/5 vertebral level in both muscles, and was over 25% in both muscles at L5/S1 (Figure 5.2). IMAT values >10% were present across the entire age range – for example, 5 out of 9 (55%) of participants aged under age 30 had IMAT > 20% for both muscles at the L5/S1 vertebral level.

Symmetry

Muscle symmetry, comparing the medians of the absolute and percentage differences between left and right pairs of measures within individuals for total and functional CSA, is shown in Table 5.2. All absolute differences were less than 1.0 cm^2, and all percentage differences less than 10%, except for the LES muscles at the L5/S1 vertebral level, and the LM muscles at the L2/3 vertebral level .

The multivariable model (Table 5.3) quantifies size differences across levels after adjusting for age, sex and BMI. Females had clinically important lower functional CSA of LM (β=-1.31, 95% CI -2.58, -0.04 for average difference between females and males) and total and functional CSA of the LES muscles (β=-2.25, 95% CI -3.84, -0.66 and β=-2.52, 95% CI -4.94, -0.10 respectively) compared with males. Sex differences for LM total and fat CSA and LES fat CSA were not statistically significant. There was only a small association between higher BMI (adjusted for mean) and larger LM total CSA (β=0.24, 95% CI -0.08, 0.39), and no other associations with BMI were identified. Similarly, age appeared to have only a small influence on the findings, after centering for the mean ages of 39.81 and 34.14 years for men and women respectively – the most clinically important being positive associations being with IMAT in both LM (β=0.51, 95% CI 0.06, 0.96) and LES (β=0.63, 95% CI 0.06, 1.20). However, inspection of scatterplots provides evidence that this association is driven by one participant aged over 60 years of age, in whom IMAT values at L5/S1 ranged from 70.1 to 100%.

Table 5.3 Muscle Symmetry for multifidus and erector spinae: median percentage and absolute differences between paired larger and smaller values, at lumbar levels L2/3 to L5/S1

	Percentage difference - total CSA (%) **Median (25th, 75th %ile)**	**Percentage difference - functional CSA (%)** **Median (25th, 75th %ile)**	**Absolute difference – Median total CSA (cm^2)**	**Absolute difference - Median functional CSA (cm^2)**
Multifidus (n=23)				
L2/3	13.28 (6.81, 15.57)	10.45 (5.01, 15.33)	0.59 (0.34, 0.88)	0.51 (0.24, 0.97)
L3/4	5.48 (2.55, 9.79)	6.47 (3.47, 11.04)	0.42 (0.21, 0.78)	0.47 (0.23, 0.77)
L4/5	5.77 (3.74, 12.94)	6.22 (3.41, 14.58)	0.54 (0.25, 1.10)	0.56 (0.29, 0.95)
L5/S1	6.85 (2.87, 12.69)	10.89 (5.25, 17.52)	0.73 (0.25, 1.34)	0.58 (0.49, 1.30)
Erector spinae (n=23)				
L2/3	5.67 (1.92, 9.68)	5.09 (1.74, 10.79)	0.94 (0.39, 2.35)	0.84 (0.23, 2.35)
L3/4	5.72 (2.17, 9.76)	8.85 (4.13, 11.45)	1.11 (0.46, 1.73)	1.30 (0.74, 1.74)
L4/5	5.89 (3.83, 8.22)	8.80 (3.57, 16.17)	0.72 (0.42, 1.41)	0.90 (0.55, 1.74)
L5/S1	15.23 (6.42, 21.49)	25.27 (15.72, 34.53)	0.80 (0.25, 1.05)	0.67 (0.35, 0.95)

Table 5.4 Multivariable model of associations of muscle CSA (total, fat, functional) and IMAT with spinal level, sex, BMI and age

	Total CSA (cm^2)		Fat CSA (cm^2)		Functional CSA (cm^2)		IMAT (%)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Multifidus								
L3/4	**1.73*** **	**1.29, 2.18**	**0.28***	**0.04, 0.52**	**1.45*** **	**1.00, 1.90**	**6.12*** **	**2.59, 9.72**
L4/5	**3.62*** **	**3.17, 4.06**	**0.74*** **	**0.50, 0.98**	**2.87*** **	**2.43, 3.32**	**8.19*** **	**4.62, 11.76**
L5/S1	**4.68*** **	**4.23, 5.13**	**1.65*** **	**1.41, 1.88**	**3.03*** **	**2.58, 3.48**	**17.17*** **	**13.61, 20.74**
Female	-0.81	-1.66, 0.05	0.50	-0.35, 1.35	**-1.31***	**-2.58, -0.04**	5.06	-5.41, 15.53
BMI (kg/m^2)	**0.24*** **	**0.08, 0.39**	0.11	-0.04, 0.26	0.13	-0.10, 0.36	0.70	-1.17, 2.58
Age (years)	-0.03	-0.07, 0.00	0.03	0.00, 0.07	**-0.07***	**-0.12, -0.01**	**0.51***	**0.06, 0.96**
Erector spinae								
L3/4	**-2.79*** **	**-3.77, -1.82**	0.36	-0.19, 0.92	**-3.36*** **	**-4.15, -2.16**	2.49	-2.15, 7.13
L4/5	**-6.17*** **	**-7.15, -5.20**	**0.59***	**0.04, 1.15**	**-6.77*** **	**-7.77, -5.77**	**7.11*** **	**2.47, 11.75**

L5/S1	**-15.11*** **	**-16.08, -14.13**	0.50	-0.05, 1.06	**-15.61*** **	**-16.61, -14.61**	**32.37*** **	**28.12, 37.40**
Female	**-2.25** **	**-3.84, -0.66**	0.26	-1.21, 1.74	**-2.52***	**-4.94, -0.10**	3.28	-9.92, 16.49
BMI (kg/m^2)	0.27	-0.02, 0.55	0.05	-0.22, 0.31	0.22	-0.21, 0.66	-0.14	-2.51, 2.22
Age (years)	0.01	-0.06, 0.08	**0.08***	**0.01, 0.14**	-0.07	-0.17, 0.04	**0.63***	**0.06, 1.20**

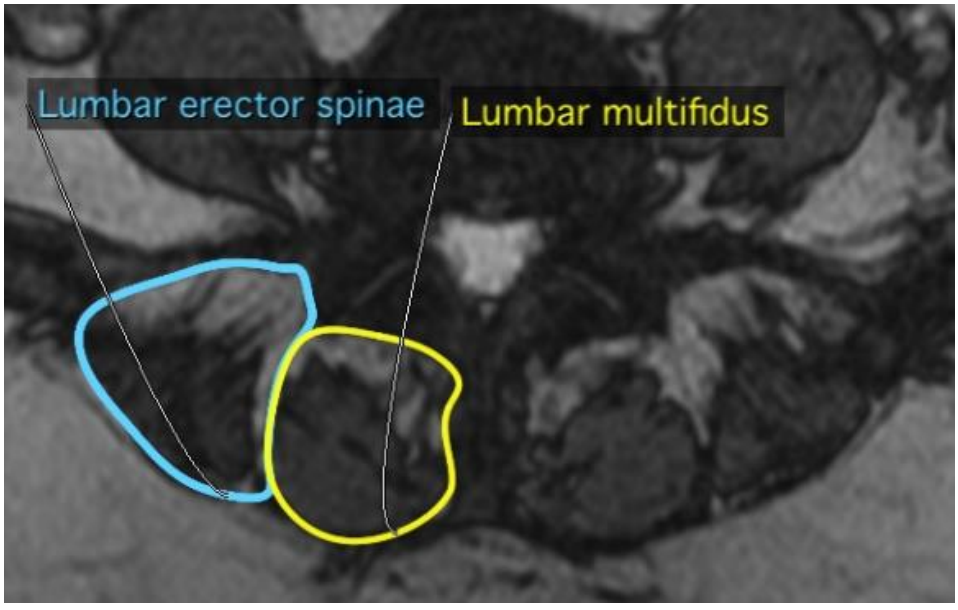
Multivariable model: each variable adjusted for other items in table; reference level is L2/3; Covariates centred for mean of age (men 39.81, women 34.14 years) and BMI (24.82 kg/m^2)

β regression co-efficient, CI confidence interval. Bold indicates significance $p<0.05$*, $p<0.01$**, $p<0.001$***

5.6 Discussion

This is one of the few studies of people with axSpA to provide details about individual lumbar muscles at multiple vertebral levels, and includes new information about the muscles at the lumbo-sacral junction. The most important and novel finding of our study was the high level of fat infiltration in both the LM and LES muscles, distributed symmetrically (Figure 5.2 and Table 5.2) in a pattern adjacent to the bony insertions of the paraspinal muscles (Figure 5.3), and present across the age range of participants. The presence of IMAT was most extensive at the L5/S1 vertebral level, where a median of approximately one quarter of the muscle mass had been replaced with adipose tissue. This is clinically important because such ectopic fat deposition (and decreased percentage of viable contractile tissue) points to impaired muscle function (diminished motor control and strength), which could be targeted using specific muscle re-training. In contrast to IMAT studies in healthy populations [19, 20] IMAT was distributed across participants with a wide range of ages, suggesting that ax-SpA associated factors may be at play. This is an avenue of inquiry that could enhance understanding of the disease and/ or contribute to maintenance of general health in people with axSpA.

Figure 5.3 Sample transverse MRI scan at L4/5 level showing location of IMAT (bright white tissue) adjacent to the bony interfaces



The findings broadly concur with those of other MRI axSpA paraspinal muscle studies. Paraspinal muscle (LM and LES muscles combined) TCSA in people with axSpA at lumbar vertebral levels L1/2 to L4/5 was smaller compared with healthy age and sex matched controls [8]. In men with axSpA, total CSA at L4/5 level only was smaller compared with controls with LBP matched for lumbo-sacral angle [10]. However, a study comparing the muscle sizes of people with non-radiographic axSpA (nr-axSpA) and those with AS found the groups had similar paraspinal TCSA [9]. With regard to the IMAT findings, IMAT assessed by semi-quantitative grading was higher in AS, compared with nr-axSpA at L4 [9], and for total paraspinal muscle CSA at L1/2 to L4/5 in people with AS, compared with controls [8]

Our finding that IMAT for both muscles significantly increased with each descending vertebral level (with the exception of LES from L2/3 to L3/4), was similar to results from larger population-based studies in people without AS [20]. However, in contrast to these studies, we did not find a statistically significant association between IMAT and BMI, and only a small association between age and IMAT. These findings support the concept that the axSpA disease process may be additive to the normal effects of BMI and ageing with regard to muscle morphology.

Implications for exercise prescription

The lumbar paraspinal muscles are considered to be postural muscles: the dominant fibre type is slow-twitch (type 1), supporting the function of constantly resisting gravitational (and other) forces (shearing, compression and traction) during upright posture, thus adding to the stability of the lumbo-pelvic region [21]. There are some similarities between the findings of our study and results reported for people with non-inflammatory LBP. Two systematic reviews confirmed evidence for an association between muscle size and ‘non-inflammatory’ low back pain (LBP) [22, 23], but the study by Ranger et al found conflicting evidence for an association between IMAT and LBP. However, a recent cross-sectional comparison of people with chronic versus recurrent LBP found significantly higher amounts of IMAT in both the LM and LES muscles in the group with chronic LBP [24]. Specific rehabilitation protocols that target motor control training of lumbo-pelvic muscles have been beneficial for reducing pain and disability and improving physical function in people with chronic LBP [25-29]. To our knowledge, there have not been any studies which have assessed motor control of the paraspinal muscles in axSpA, or the effect of an intervention designed to improve their size, quality and function and this warrants further investigation.

A further consideration is the consistent location of the IMAT changes we found, in the deeper aspects of the muscles, that is, adjacent to the bony surfaces. Since LM is thought to be particularly adapted to a proprioceptive role, as evidenced by the high density of muscle spindles in the deep portion of the muscle [30,31], testing for an association between IMAT and this function could again reveal a useful therapeutic pathway.

Lastly, consideration of the respective roles of the muscles in spinal stability and prime movement may prove worthwhile. One role of LM is to maintain the lordosis of the lumbar spine, which is thought to be important in controlling shearing and compression forces in the spine [32]: it therefore seems plausible that exercises specifically aimed at maintenance and control of the lumbar lordosis in axSpA may be beneficial for symptom management.

Implications for disease understanding

The relationships between the observed changes in morphology of the lumbar paraspinal muscles, and biomechanics, inflammation and physical function in axSpA are likely to be complex and could be interpreted in relation to a range of theories around axSpA pathophysiology.

The primary pathological change in axSpA is enthesitis [33,34]. In a model described by McGonagle et al, local micro-trauma, secondary to a loss of joint stability at entheseal sites in predisposed individuals, has been postulated as a causative trigger for adjacent osteitis and the subsequent establishment of axSpA [35, 36], and as a factor in structural progression (that is, syndesmophyte formation and bony ankylosis) in established axSpA [37]. The latter authors propose that the type and intensity of physical activity is crucial to the maintenance of optimal biomechanical stress in axSpA – that is, there should be sufficient muscle activity to maintain stability, but not so much as to produce excessive compression. Our findings support this concept: due to the association between paraspinal muscle quality and isometric strength [38], a reduction in functional paraspinal muscle CSA, and its replacement by adipose tissue, could be a source of increased biomechanical stress in the lumbo-pelvic region.

One explanation for our findings could be that the muscles themselves are a local target tissue for the disease process, with migration of inflammatory pathophysiology adjacent structures into the muscle tissue itself. Biopsy studies of the paraspinal muscles in axSpA showed varying degrees of type I and II fibre atrophy, and fatty and fibrous connective tissue infiltration [39-41]. Our finding that the presence of IMAT was most prevalent at the lower lumbar levels, and involved both the LES and LM muscles in a bilateral, and largely symmetrical, manner, invites consideration of a local, bilaterally distributed, inflammatory

environment that includes muscle tissue. This could account for the clinically observed rapid symptomatic improvement that some individuals experience with large range mobility exercises [42].

Alternatively, these muscle changes could represent local muscle disuse atrophy, secondary to pain and/or structural progression, such as syndesmophytes, in axSpA. Supporting this concept, in another MRI study the total and functional CSA of the paraspinal muscles at the L4/5 vertebral levels was significantly less in those with axSpA who had a decreased lumbar lordosis/ increased sacral slope, compared with matched axSpA participants without spinal deformity [10]. Systematic reviews provide evidence of paraspinal muscle atrophy, ipsilateral to the side of chronic unilateral LBP compared with healthy controls [22], with changes preferentially affecting the LM muscles [23]. However, since IMAT was distributed across both the LES and LM muscles in the present study, pain sequelae alone appears unlikely to provide a complete explanation.

Rather than being a local indicator of disease process or disuse, the muscle changes in our study could be related to generalised (whole-body) inflammation-mediated, accelerated sarcopaenia [42]. Previous evidence examining this concept has been equivocal: sarcopaenia has been identified in some axSpA studies [43-46] but not in others [47,48]. However, whilst there are a number of reasons why investigation of generalized IMAT is important [11], its presence alone does not explain the specific location of IMAT (at the lower lumbar vertebral levels and adjacent to the bony interfaces) seen within the paraspinal muscles in our study.

Strengths/ weaknesses

This pilot study adds to knowledge about paraspinal muscles in axSpA, by providing detailed quantification of size, symmetry and IMAT across multiple lumbar levels. Due to the specific alignment of the MRI scans, we were able to obtain previously unidentified information about the L5/S1 vertebral level, which in our study showed the most change. However, because of the small, exploratory nature of the study, it was not possible to stratify participants into groups (such as those with bridging sydesmophytosis versus those with no ankylosis), or to reliably examine a number of the potential associations in more detail. As there was not a control group (or normative data available using similar methodology), a comparison with a ‘non axSpA’ sample was not possible, and since this was a cross-sectional study, cause and effect relationships could not be determined. It is therefore recommended that future investigation includes group stratification and examines longitudinal changes. Lastly, MRI

may not differentiate between, or detect, all relevant tissue pathology – for example, intra-muscular triglyceride deposition [49] or other microscopic changes.

5.7 Conclusion

People with axSpA have high levels of intermuscular adipose tissue in both the LM and LES muscles, which is largely symmetrical and most pronounced at the lower lumbar vertebral levels. A number of potentially complex relationships between the muscle changes, biomechanics and disease pathogenesis and progression are plausible. Regardless, these data support the need to develop and test potential exercise interventions targeting these muscles in axSpA, including biomechanical effects.

Supplementary Table 5A: Medians and 25th, 75th percentiles for LM CSA and IMAT by sex, level and side

Level	Total cross sectional area (TCSA), cm^2		Fat infiltrate CSA, (FatCSA) cm^2		Functional (FunCSA), cm^2 (TCSA-FatCSA)		Intermuscular Adipose Tissue (IMAT) %	
Males (n=16)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	5.08 (4.48, 6.84)	4.69 (4.18, 6.71)	0.00 (0.00, 0.25)	0.00 (0.00, 0.20)	4.78 (3.93, 6.84)	4.61 (4.10, 6.71)	0.00 (0.00, 5.04)	0.00 (0.00, 3.49)
L3/4	6.83 (6.69, 7.73)	6.85 (6.24, 7.56)	0.26 (0.00, 0.90)	0.10 (0.00, 0.30)	6.66 (6.34, 7.30)	6.51 (6.00, 7.19)	3.74 (0.00, 6.37)	1.51 (0.00, 4.12)
L4/5	9.20 (8.10, 10.34)	8.71 (8.02, 9.92)	0.50 (0.00, 0.77)	0.22 (0.00, 1.43)	8.29 (7.48, 9.09)	8.29 (7.28, 8.92)	5.50 (0.00, 8.20)	3.15 (0.00, 14.22)
L5/S1	10.15 (8.91, 11.08)	9.76 (9.32, 10.52)	1.27 (0.55, 3.25)	1.15 (0.44, 2.17)	7.96 (7.47, 9.97)	8.44 (7.37, 9.63)	11.76 (5.77, 29.82)	11.84 (7.20, 22.20)
Females (n=7)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	3.37 (3.09, 6.09)	4.09 (3.43, 7.15)	0.00 (0.00, 0.83)	0.00 (0.00, 0.15)	3.37 (2.63, 5.35)	3.86 (3.43, 5.13)	0.00 (0.00, 15.09)	0.00 (0.00, 3.67)
L3/4	6.56 (4.35, 7.69)	6.82 (5.00, 8.05)	0.53 (0.32, 1.00)	0.30 (0.23, 0.45)	5.15 (3.77, 6.84)	5.09 (3.99, 7.31)	8.66 (5.84, 15.17)	5.47 (3.21, 6.52)

L4/5	8.49 (7.87, 8.89)	8.82 (6.52, 9.02)	1.08 (0.48, 2.11)	0.82 (0.33, 1.50)	6.78 (5.82, 7.52)	6.57 (5.51, 8.09)	13.18 (7.12, 23.77)	11.03 (5.13, 15.91)
L5/S1	10.49 (8.89, 10.59)	9.33 (8.67, 10.62)	3.02 (1.82, 4.06)	1.78 (1.42, 3.32)	6.53 (5.48, 7.73)	7.26 (6.01, 8.68)	30.89 (24.92, 38.34)	17.10 (16.32, 35.55)

Total (n=23)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	4.93 (3.69, 6.34)	4.42 (4.08, 6.75)	0.00 (0.00, 0.47)	0.00 (0.00, 0.17)	4.76 (3.37, 6.10)	4.20 (3.80, 6.68)	0.00 (0.00, 9.36)	0.00 (0.00, 3.67)
L3/4	6.76 (6.50, 7.69)	6.82 (6.14, 7.67)	0.36 (0.00, 0.67)	0.23 (0.00, 0.36)	6.45 (5.15, 7.03)	6.38 (5.14, 7.22)	5.27 (0.00, 10.61)	3.32 (0.00, 5.48)
L4/5	8.80 (7.95, 10.12)	8.41 (7.67, 9.64)	0.53 (0.27, 1.87)	0.58 (0.14, 1.50)	7.57 (6.96, 8.92)	7.93 (6.20, 8.87)	6.35 (1.87, 16.52)	6.46 (1.52, 15.30)
L5/S1	10.16 (8.89, 10.64)	9.07 (9.29, 10.62)	1.81 (0.65, 3.39)	1.42 (0.91, 2.20)	7.73 (6.53, 9.30)	8.06 (7.14, 9.60)	18.29 (5.98, 33.91)	15.25 (8.90, 23.47)

Supplementary Table 5B: Medians and 25th, 75th percentiles for LES CSA and IMAT by sex, level and side

Level	Total cross sectional area (TCSA), cm^2		Fat infiltrate (FatCSA)CSA, cm^2		Functional (FunCSA), cm^2 (TCSA-FatCSA)		Intermuscular Adipose Tissue (IMAT) %	
Males (n=16)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	18.97 (17.72, 25.41)	21.28 (17.64, 24.54)	0.13 (0.00, 1.47)	0.10 (0.00, 1.05)	18.97 (17.52, 24.33)	20.89 (17.25, 23.09)	0.56 (0.00, 7.11)	0.48 (0.00, 4.44)
L3/4	17.17 (13.59, 20.48)	16.15 (14.54, 20.28)	0.21 (0.01, 0.90)	0.07 (0.00, 0.66)	15.83 (12.96, 19.12)	15.70 (13.87, 19.68)	1.26 (0.04, 6.14)	0.44 (0.00, 3.75)
L4/5	12.33 (10.91, 13.45)	13.02 (11.14, 15.09)	0.81 (0.17, 1.49)	0.77 (0.25, 1.22)	11.03 (9.79, 13.37)	11.97 (10.15, 14.00)	7.36 (1.19, 12.48)	5.61 (1.74, 10.37)
L5/S1	3.83 (3.41, 4.65)	3.92 (3.42, 4.51)	0.88 (0.49, 1.87)	0.95 (0.44, 2.15)	2.52 (2.19, 3.50)	2.77 (1.82, 3.64)	25.63 (10.99, 43.40)	25.17 (12.40, 50.16)
Females (n=7)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	13.67 (12.06, 18.29)	13.88 (11.83, 18.88)	0.22 (0.00, 1.38)	0.16 (0.00, 0.50)	13.67 (12.06, 14.66)	13.72 (11.83, 16.01)	1.64 (0.00, 7.31)	1.17 (0.00, 2.54)
L3/4	15.64 (11.82, 16.44)	14.83 (10.66, 16.62)	0.65 (0.00, 1.38)	0.51 (0.00, 0.77)	12.21 (11.30, 14.98)	12.42 (10.62, 15.51)	4.16 (0.00, 8.37)	3.04 (0.00, 4.71)

L4/5	14.05 (10.51, 15.06)	14.34 (10.93, 14.70)	1.39 (1.18, 4.00)	0.73 (0.43, 4.14)	10.97 (8.68, 12.90)	11.03 (10.30, 13.78)	12.79 (8.20, 26.39)	5.85 (3.03, 28.34)
L5/S1	4.33 (3.77, 5.27)	3.53 (2.48, 5.27)	1.94 (1.02, 3.07)	1.50 (0.73, 2.32)	2.04 (1.40, 3.09)	2.05 (1.54, 2.96)	47.14 (23.56, 72.83)	45.38 (20.76, 54.67)

Total (n=23)								
	Right	Left	Right	Left	Right	Left	Right	Left
L2/3	18.50 (15.74, 22.99)	18.88 (16.01, 22.27)	0.20 (0.00, 1.34)	0.11 (0.00, 0.70)	17.98 (14.46, 22.99)	18.75 (14.72, 22.19)	0.81 (0.00, 7.31)	0.60 (0.00, 3.71)
L3/4	16.05 (13.10, 19.24)	15.96 (14.08, 19.08)	0.49 (0.00, 1.19)	0.36 (0.00, 0.71)	14.86 (12.31, 17.93)	14.48 (12.42, 18.33)	3.55 (0.00, 7.25)	2.78 (0.00, 4.12)
L4/5	12.50 (10.71, 14.47)	13.16 (10.93, 14.70)	1.11 (0.27, 1.87)	0.76 (0.27, 1.33)	10.97 (9.27, 13.02)	11.59 (10.30, 13.78)	8.57 (1.49, 15.52)	5.78 (1.79, 10.42)
L5/S1	4.00 (3.55, 4.66)	3.92 (2.92, 4.57)	1.46 (0.64, 2.13)	1.28 (0.49, 2.32)	2.46 (2.03, 3.09)	2.70 (1.69, 3.06)	38.86 (18.16, 68.74)	35.18 (12.81, 52.26)

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Chapter 6: Summary

6.1 Background and aims of the thesis

Regular and lifelong exercise is frequently recommended to people diagnosed with axSpA – however, as discussed in chapter 1, details regarding the best type, dosage and setting are less often provided. For the individual concerned, implementing this advice can therefore be daunting and difficult [1]. Some find great benefit, whilst others are unable to change their exercise habits and continue with low levels of physical activity [2]. Particularly for those people who have little belief in the value of exercise, it perhaps seems unreasonable to expect such a large lifestyle change, without a complete evidence base. And for the health professional tasked with 'guiding' exercise planning and skills development, evidence and recommendations on which to base interventions is lacking. This thesis therefore aimed to identify and analyse the current evidence for exercise in axSpA, develop more specific recommendations to guide the work of HPs, and explore the morphometry and quality of the lumbar paraspinal muscles - with a view to informing future trials of exercise interventions.

6.2 Major findings and implications

Strength of evidence for exercise in axSpA

The study presented in Chapter 3 comprised eight systematic reviews and meta-analyses where RCTs were available, in response to the clinical questions developed by an expert panel. Overall, the results confirmed the previous Cochrane systematic review [3], that is, a consistent trend for moderate effect sizes in favour of exercise for AS, based on Level 1B evidence – that is, pooled results of RCTs with less than 50 participants per group. There was an increase in the number of high quality trials, when measured by a scale of trial internal validity (PEDro) [4]. However, the subsequent analysis presented in Table 1.2 demonstrates poor therapeutic validity (design of the actual exercise program under investigation) in 55% of the included RCTs. This problem contributes to the evidence gaps noted below.

Individual recommendations

Ten recommendations to provide more details about exercise prescription in AS were developed, supported by a number of Practice Points where there was consensus derived information that the panel considered clinically important. The initial results were tested by

surveying healthcare providers and people with axSpA (chapter 3), and the wording adjusted accordingly. The subject and context for each recommendation is listed as follows:

1. **Assessment** – to inform exercise prescription. Recommendations 1 and 2 are the first to describe how exercise prescription should be individually tailored according to axSpA assessment findings.

2. **Monitoring** – to review effectiveness, inform exercise program adjustment and assist adherence.

3. **Safety** – to describe precautions. This is one of the few recommendations to highlight the risks of inappropriate exercise in people with advanced axSpA: largely due to the increased incidence of falls and spinal fracture linked to the combination of spinal ankylosis, osteoporosis and decreased balance. This recommendation was specifically reinforced in a review of spinal fractures related to AS [5].

4. **Disease management – exercise should be continued with bDMARDS -** Although there was insufficient evidence that exercise alone can be disease modifying, several RCTs demonstrated a synergistic effect when exercise is performed concurrently with bDMARD therapy. This is important, as the advent of bDMARDs has placed a greater emphasis on pharmacological disease management – perhaps at the expense of non-pharmacological strategies - despite findings that there can be a reduction in physical activity levels and gain in adiposity / body mass index, following commencement of these drugs [6, 7].

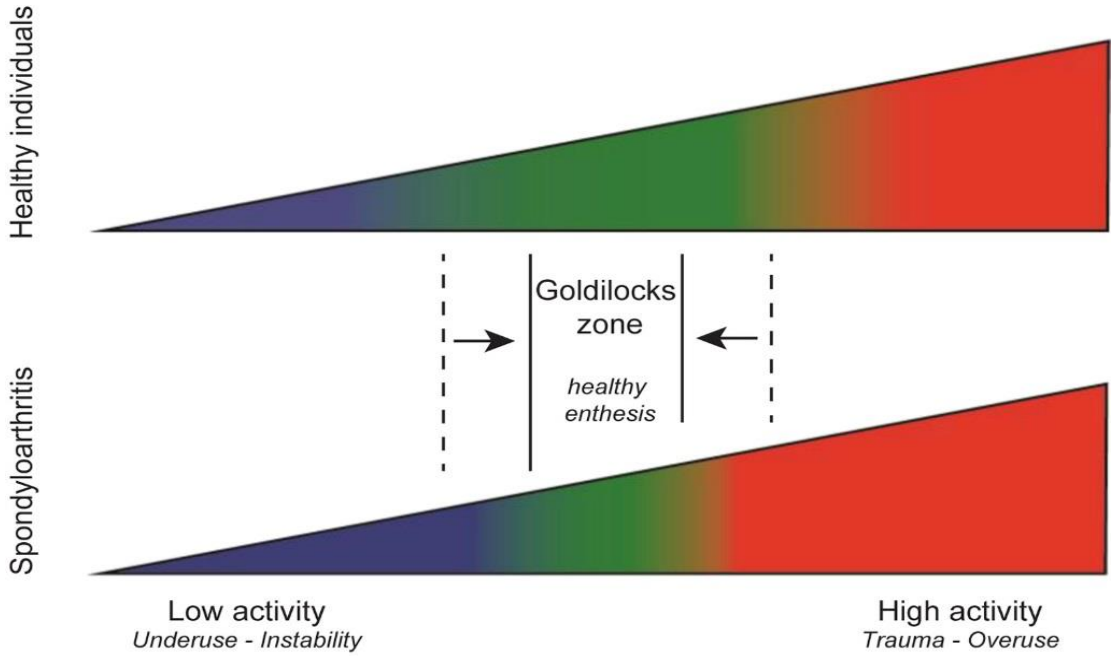
5. **AS-specific exercise: mobility** - This recommendation supports the continuation of 'traditional' mobility exercises, as there is now a considerable body of evidence supporting their effectiveness.

6. **AS-specific exercise: other** -The purpose of this recommendation is to highlight the importance of including other exercise types, such as stretching, strengthening, cardiopulmonary and functional fitness, to build a balanced program.

7. **Physical activity -** There was no evidence that one type of activity is superior to another for axSpA. The relationships between physical activity, inflammatory autoimmune disease and the local manifestations of axSpA require further clarification, however, it is now clear that appropriate amounts of exercise can be anti-inflammatory in effect [8].

8. **Dosage** - The conclusion was made that mobility exercise needs to repeated frequently and consistently (at least on most days). The need to address dosage for different exercise types and aim for physiological effectiveness whilst simultaneously adapting dosage to an individual's disease presentation, and changing needs, was also recognised. This concept of "just right" dosage has recently been discussed in the context of new information concerning axSpA biomechanics [9] (Figure 6.1).

Figure 6.1 Postulated 'ideal' exercise dosage range in healthy people and those with, or susceptible to, axSpA



Blue zone = low physical activity/ inadequate muscle strength
Red zone = high physical activity/ musculo-skeletal 'overload'.
It is proposed that the "Goldilocks" or 'just right' zone is smaller for those with axSpA – range represented by the solid lines, compared to those without axSpA, represented by dotted lines

From Debusschere (2018) ***Born to run: The paradox of biomechanical force in spondyloarthritis from an evolutionary perspective****; used with permission (granted 10/10/18)*

9. **Adherence.** The importance of addressing adherence as part of therapy was acknowledged - although the supporting evidence was mainly found in the general arthritis literature. A more recent RCT, however, has assessed the impact of a behavioural change intervention in axSpA, finding that physical activity, mobility and quality of life improved significantly, and this improvement was maintained at three months [10] – thus directly supporting this recommendation.

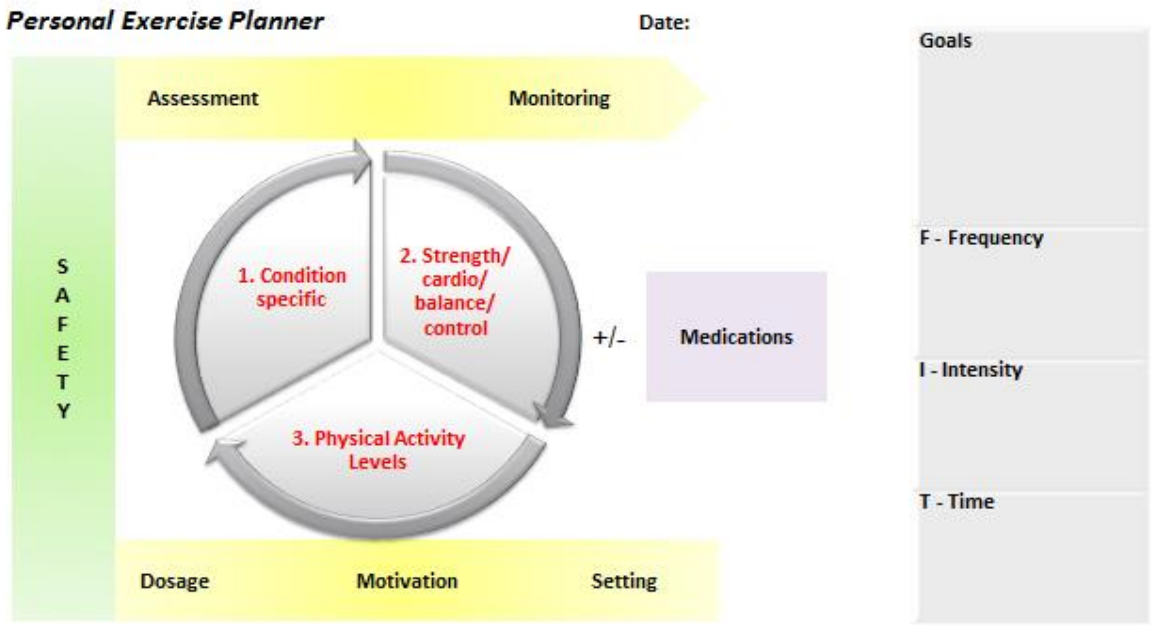
10. **Setting.** Several RCTs compare exercise settings, rather than exercise types, and the CS panel concluded that a number of settings, such as in-patient or group physiotherapy or hydrotherapy, were difficult to access in Australia. Consensus opinion also prioritised patient choice and enjoyment in association with sustained adherence. For these reasons, a consensus-based (rather than evidence based) recommendation (CBR) was made regarding exercise setting.

The recommendations appear to be translating into clinical practice, having been referenced in the TGL Therapeutic Guidelines: Rheumatology (3rd Edition) [11], and recommended by the patient support groups in the USA and Germany, including translation into the German language by the latter group.

Framework

A novel feature of the paper presented in Chapter 3 was the representation of the requirements for exercise prescription in a framework (Figure 3.1). The purpose of the framework is to highlight the relationship of, and interaction between, the different components. For example, exercises which improve thoracic spine mobility may allow better biomechanical positioning of the shoulder girdle muscles, so that muscle strength may be improved. This in turn may enhance motivation to perform a complementary physical activity, such as swimming – leading to increased lifestyle integration of exercise and thus facilitating sustained adherence. The arrows indicate that the process is dynamic and requires ongoing review and progression, in order to optimise physiological effectiveness. This framework has been cited by the American Spondylitis Society [12] and been used for teaching purposes by presentation at specialist physiotherapy courses in the United Kingdom, and adapted as patient education resource (Figure 6.2).

Figure 6.2 Adaptation of the exercise framework (Figure 3.1) as an exercise planning tool



Paraspinal muscles in axSpA

A significant gap in the evidence for exercise in SpA was identified – there was a paucity of information regarding exercises that might strengthen muscles, including those that would be physiologically effective in strengthening trunk muscles. It is generally accepted that strengthening exercises are important for the maintenance of health, especially from middle life onwards [13]. However, in order to design axSpA-specific, effective exercise regimes, more information is also required about the muscles themselves, and any changes they undergo as part of, or consequent to, the inflammatory disease process. This foundation knowledge is particularly important within the lumbo-pelvic region, where the complex biomechanics play an essential role in normal movement, and where enthesitis (the fundamental pathophysiological disease process in axSpA), is thought to be influenced by biomechanical strain.

Our study to examine the paraspinal muscles in axSpA, presented in Chapter 5, therefore provided some novel information,that points to potentially productive lines of enquiry

regarding future trials of axSpA-specific strengthening exercises. The major finding is that lumbar paraspinal muscle tissue is commonly replaced by adipose tissue. This change is apparent symmetrically, in both main muscle groups and most pronounced at the lower lumbar levels. IMAT is a significant predictor of muscle function and overall mobility and physical function. In the lumbar spine, such changes make it likely that the muscles are weaker and that their function as spinal stabilisers is diminished, due to the reduction in functional muscle mass. Since IMAT and other muscle changes are potentially modifiable by exercise, there is a rationale to support potential improved biomechanics in axSpA, linking back to the relationship between biomechanical stress and disease process. Of particular interest is the concept of a 'just right' amount of biomechanical compression or loading, in which the paraspinal muscles play a key role.

Recent research attention has also highlighted the presence of intermuscular adipose tissue as an indicator of systemic inflammatory state, general wellness and longevity [14-15]. Therefore, in addition to indicating a target for further evaluation of novel exercise strategies, the results may also have implications for our understanding of axSpA pathophysiology and its relationships with co-morbidities, such as osteoporosis and cardiovascular disease [16].

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Chapter 7: Future directions

This thesis has highlighted a number of limitations and research gaps regarding exercise for people with axSpA. The high personal commitment for individuals in adapting to lifelong exercise advice, high socioeconomic costs of this disease, recent insights into axSpA biomechanics, and increased understanding of the importance of physical exercise for the maintenance of health all paint to the need for greater clarity in exercise advice.

7.1 Research recommendations

Exercise advice

In general, larger RCTs would allow for stratification of exercise interventions for different groups: appropriate exercise advice for a young adult who has low disease activity, and good axial mobility, is likely to be different to that for an older adult who has total spinal ankylosis. No studies were identified that specifically targeted either group. Addressing the paucity of longer duration studies, and including longitudinally measured outcomes, would provide much needed insight into the interactions (if any) between exercise and axSpA structural progression and disease activity. The role of emerging new serum markers for inflammation in evaluating the relationship between exercise and inflammation in axSpA [1], could also be explored. Greater attention should be paid to the design of exercise programs, in particular, dosage. Chapter 1 discussed how exercise dosage may require initial adaptation (reduction) due to the presence of symptoms, primarily pain, and yet exercise dosage in many studies was insufficient to produce the physiological change that was being measured. Studies of longer duration would allow assessment of interventions that started from a lower exercise baseline and were appropriately progressed to a more physiologically effective dose.

The largely theoretical concern around exercise type and intensity in relation to biomechanical force in axSpA is encapsulated in a recent review [2]. Clarification is highly important, in order that the message about optimising exercise type does not inadvertently generate misinformation, with the unintended consequence of fewer people with axSpA benefitting from exercise. Thus evaluation of an exercise program that specifically aims to improve spinal stability without adding to compressive biomechanical stresses, is highly desirable.

Exercise Planning

People with other arthritis/ inflammatory conditions experience similar challenges when attempting to integrate exercise into their lifestyles as people with axSpA [3-6]. The exercise framework presented in chapter 3 is adaptable as a client-centred planning tool, and this could be evaluated with people who have a range of conditions, with a view to facilitating safe and effective exercise practice across the broader population with chronic conditions.

The impact of exercise on disease

Chapter 5 discussed the paucity of information regarding muscle pathophysiology in axSpA, and its possible relationship with disease development and progression. A further unknown is whether the disease has any impact on trunk muscle motor control (or *vice versa*) - that is, the ability to appropriately recruit muscles in a coordinated manner, in order to continuously adjust to compression/ shearing forces. This could be tested using real-time ultrasound techniques that have been validated in other groups [7, 8]. Further MRI studies, perhaps examining trunk muscle volume longitudinally, could elucidate changes, and their relationship to physical activity, structural progression and comorbidities such as spinal osteoporosis.

Exercise, bDMARDs and cost-effectiveness

In the era of bDMARDs, many countries (including Australia) have seen a transition of rheumatology care from a hospital or rehabilitation centre in-patient setting, to out-patient or community care. At the same time, the large effect size of bDMARDs on disease activity (for most people), has led to a decreased emphasis on exercise as an integral management strategy [9]. A number of reasons why it is be important to retain knowledge about, and funding for, exercise advice have been discussed in this thesis. However, the large disparity in funding (for both research and interventions) between pharmacological and non-pharmacological therapy is only likely to be narrowed if there is sufficient high-quality evidence for the effectiveness of exercise. Further research into the interactions of exercise and bDMARDs could provide useful information for funders.

It is known that exercise and bDMARDs have some similarities in effects of action at microscopic level, such as inhibition of pro-inflammatory cytokines [10] and that they appear synergistic in effect [11]. The latter studies have led to the suggestion that exercise may enhance the cost-effectiveness of bDMARDs, by enabling dose reduction [12] – such a

finding could support the retention of exercise as integral to disease management in axSpA. It is also plausible that adequate exercise may allow for bDMARD dose tapering - increasing cost effectiveness and potentially allowing easing of the criteria for accessing these drugs.

7.2 Conclusion

Systematic reviews and meta-analysis provided sufficient information to inform the development of ten specific recommendations to guide health professionals' exercise advice for people with axSpA. The recommendations were the first to specifically address: exercise-related assessment and monitoring; safety; concurrent medication use; mobility, functional (including strength) and cardio-respiratory exercise; dosage; adherence and setting. A framework was developed that facilitates adaptation of the recommendations to each individual's presentation. Information about muscle pathophysiology and function in axSpA was prominent amongst a number of identified knowledge gaps. An exploratory study indicated that paraspinal muscle fitness is sub-optimal and thus is a potential target for future axSpA exercise studies.

7.3 References

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